Reversible Renal Insufficiency

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DIAGNOSIS AND TREATMENT

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Preface

For the past ten years we have been concerned and occupied with the problem of reversible renal insufficiency on the wards of the Cook County, Mount Sinai, and West Side Veterans Administration Hospitals of Chicago We studied several facets of the problem experimentally, and the results of our investigations have been published

Although reversible renal insufficiency has been known for the past three decades as 'extrarenal azotemia," it is only during the past fifteen years that a huge body of clinical and experimental literature dealing with the subject has appeared During this period we have labored to keep abreast and digest the voluminous literature and its many conflicting and overlapping conclusions The flood of published material is ever rising, and, like the Sorcerer's Apprentice, we are about to be submerged We believe, therefore, that a survey of the entire field in the light of our own experience is a timely and worthwhile endeavor As much material as possible is reviewed, including the several excellent monographs and volumes dealing with individual aspects of reversible renal insufficiency

Our title has been chosen to emphasize the potential reversibility of both acute and chronic renal insufficiency associated with many diverse conditions Although the term "acute renal failure" is widely used, we prefer the term acute (or chronic) renal insufficiency because failure' implies bankruptcy of function, whereas "insufficiency" connotes, in truth, a more hopeful prognosis

Our major objective is to enable the clinician to differentiate acute and chronic conditions associated with reversible renal insufficiency from primary renal disorders which progress inexorably to fatal uremia Secondly, we make a decided effort to change the

all too hopeless attitude toward the patient with acute and chronic renal disease, and emphasize that with careful thought and patience, proper treatment often results in reversibility and prolongation of life

To achieve our objective, we considered two divergent plans first, to organize the material in a comprehensive, encyclopedic form which would be of value to nephrologists, physiologists, and internists, and second, to write a concise and simple monograph which would be of value to medical students, general practitioners, and specialists in surgical fields wherein this problem is most frequently encountered As is often the case, we resolved our conflict by compromise and we have included material of interest to all groups

We wish to thank the staff members of the Cook County, Mount Sinai, and the West Side Veterans' Hospitals for their cooperation in granting us permission to study their cases, especially the following physicians Drs Arnold Black, Irving Dvore, Louis Feldman, Joseph Gault, Harry Isaacs Herbert Lakin, Aaron Neiman Irving Neims, Hans Popper, Henry Rappaport, Sidney Rosenberg, and Hyman Zimmerman

We also wish to thank Dr Harry F Weisberg for his valuable suggestions, Mrs Evelyn Palmer and Mr Thomas Scanlan for photographs, and we are grateful to The Chicago Medical School for furnishing office facilities and secretarial help

Introduction

That the function of the kidney may be vitally affected in a variety of disease states which are not primarily renal in origin has long been known Kidney lesions were described as associated with burns, hemoglobinuria, shock, and acute infections as far back as 1823 [70] Such terms as acute Bright's disease, acute parenchymatous nephritis, and acute tubular nephritis were histologically descriptive terms applied to these lesions When the modern classification of kidney disease by Volhard and Fahr[388] omitted these entities, the entire field was generally neglected

In a comprehensive article in 1938, Jeghers and Bakst[167] categorized the knowledge to date Under the term, "extrarenal azotemia," they described the basic mechanisms involved, and emphasized the comparatively minor nature of the histologic changes frequently observed There seems then to have been a hiatus in investigative work in this area until curiosity was again stimulated by an appearance in the literature of a description of the "crush syndrome" by Bywaters[52] in England in 1941

Following this, because of its wartime importance, the relation of shock to renal disturbance assumed general interest Lueckė,[213] in 1946, studied particularly the renal pathology of shock and introduced the term, "lower nephron syndrome"

Despite overwhelming evidence to the contrary, with histologic studies demonstrating that pathologic alterations range from complete absence to extensive damage involving the glomeruli, interstitial tissues, and all portions of the nephron structure, the appealing designation of Lueckė,[213] "lower nephron nephrosis," is tenaciously entrenched as a "catch all" loosely applied to all forms of acute potentially reversible azotemic, anuric, and oliguric states

A voluminous literature has accumulated under various titles,

i e, extrarenal azotemia, prerenal azotemia, traumatic kidney, shock kidney, crush syndrome, hemoglobinuric nephrosis, reversible uremia, acute renal insufficiency, toxic nephrosis, lower nephron syndrome, traumatic uremia, acute tubular necrosis, and necrotizing nephrosis This list is by no means complete, but the multiplicity is indicative of the need for nosologic reorganization

It is unfortunate that each author in this field, in a well meaning attempt to clarify pathogenesis, chose to coin new terminology, i e, ' burn nephritis' (Marchand,[225] 1908), ' crush syndrome" (Dunn,[89] Bywaters,[52] 1941), renal anoxia' (Maegraith,[217] 1945, the authors,[121] 1951), hemoglobinuric nephrosis" (Mallory,[220] 1947), 'the ischemuric and nephrotoxic kidney" (Oliver,[275] 1951), and "acute renal failure (Swan and Merrill,[370] 1953, Grollman,[138] 1954, and Strauss and Raisz,[368] 1956)

Previously we preferred to use the term, "renal anoxia,' suggested by Maegraith[217] since anoxia seems to be the common denominator in these conditions However, we have since adopted the all inclusive term, acute renal insufficiency

In 1947, Trueta and his group[381] added to the understanding of the pathologic physiology involved by demonstrating the importance of neurogenic factors in animals subjected to shock

Van Slyke[384] and others[194] enhanced our knowledge of renal physiology by renal clearance studies following shock in dogs and human subjects

In 1951, Oliver s[275] microdissection of nephrons contributed enormously to the understanding of the morphology of these conditions, and most recently, Swan and Merrill[370] published extensive studies on the clinical course

The importance of acute reversible renal insufficiency is evident in its ubiquity, for it has been observed by physicians in every phase of medicine and its specialties Indeed, there is no phase or specialty of medicine in which this syndrome may not be encountered, wherefore a knowledge of this subject is necessary for every practicing physician

In military medicine, post traumatic acute renal insufficiency

has been a major problem In World War II 40 per cent of one group of severely wounded patients developed acute post traumatic renal insufficiency with a fatality rate of 90 per cent among the severely oliguric[161]

With such a diversity of conditions a common pathogenesis is probably non existent More than one mechanism is commonly involved Certain mechanisms such as renal ischemia however occur so frequently that they may be considered fundamental A thorough understanding of the pathogenesis and an awareness of the various disease states in which acute renal insufficiency can occur will lead to earlier diagnosis and more effective treatment When detected early this condition may be reversible whereas later the mortality rate is high

While this work deals primarily with potentially reversible acute renal insufficiency we believe that a more complete purpose will be served by including a survey of potentially reversible chronic renal insufficiency The common denominator in many of these conditions is a disturbance of calcium metabolism resulting in nephrocalcinosis Although most patients afflicted with chronic renal insufficiency slowly deteriorate and ultimately expire occasionally chronic renal disease is caused by a condition which can be arrested or improved if not completely reversed It is not our intention to review the diagnosis and treatment of those inexorably fatal cases although with proper management life can be prolonged for months or even years as illustrated by Merrill[370] in his recent volume Rather it is our purpose here to review those conditions associated with chronic renal insufficiency which are amenable to arrest amelioration or cure

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Part I

Reversible Acute Renal Insufficiency

I

Pathology of Acute Renal Insufficiency

Historic Background

Histologic findings in acute renal insufficiency have been controversial, both with respect to microscopic details and the portions of the nephrons principally involved In 1946, Luecke[213] suggested that the pathologic changes in all cases are localized in the distal segment of the nephron, and coined the term lower nephron nephrosis Such precise localization has seemed to us[121] and others[52, 53, 73, 115, 131, 152, 217, 231] incompatible with the known physiologic, histologic, and experimental facts

Histologic changes within the lower segment of the nephron, as described by Lueckė,[213] consist of focal degeneration or necrosis of the tubular epithelium, heme casts, secondary inflammatory reactions of the adjacent stroma, and thrombosis of the thin walled veins Lueckė[213] described this picture not only in conditions associated with shock but also those associated with sulfonamide intoxication, mushroom poisoning, acidosis, alkalosis, and dehydration This concept, of damage localized specifically at the distal segment, directed Lueckė[213] to the term lower nephron nephrosis which immediately became a medical cliché

Prior to Lueckė s concept,[213] pathologic alterations of the kidney in shock or burn cases were described as involving all areas of the kidney grossly, and the entire nephron histologically Some reports designated the proximal convolution[231] as the portion of the nephron most damaged, but alterations were also observed in the distal convolution,[270] the glomerulus,[115] the interstitial tissue, and the blood vessels

Early Pathologic Descriptions

Moon,[253 254 255] in a description of renal insufficiency associated with shock, confirmed the histologic findings of previous investigators[18 406] in his statement

> The microscopic picture presents varying degrees of changes within a regular pattern Usually, hyperemia of the glomerular tufts and of the intertubular vessels is conspicuous Sometimes, capillary hemorrhages are present Frequently, amorphous material is seen in the capsular spaces The epithelium of the convoluted tubules shows acute degeneration ranging to necrosis When death occurs after several days the cells are low or cuboidal in shape and the lumens are wide The cytoplasm is granular, more advanced degeneration is indicated by vacuolization of the cytoplasm or by disintegration of the cells Nuclear changes, especially karyolysis and hyperchromatism, are conspicuous Usually, these changes are more pronounced in the upper segment, *sometimes in the lower, but in general all portions of the convoluted* tubules are affected Plugs of debris often form in the lumens of the lower segments because such debris originating in the upper portion of the nephron, collects in the narrow lumen of the lower portion Hyaline droplets may form in the cytoplasm when degeneration is advanced the lumens may contain masses of this deep red material when the cells containing it have disintegrated Hyaline, granular, and sometimes [illegible]

In 164 experimentally burned dogs, Christophe[59] described manifestations of an acute glomerular nephritis ' characterized by oliguria, *albuminuria casts, and a rise in non protein nitrogen* He described changes identical to those of acute glomerular nephritis, consisting of extensive glomerular congestion and tubular degeneration

Sevitt[337] studied renal tissues obtained from 86 fatally burned patients of all ages, and concluded that fifty to sixty per cent of such patients have some form of tubular necrosis He reported that *necrosis* of the proximal convoluted tubules is more common in elderly persons, while distal tubular necrosis is more frequent in children and young adults

Martineau and Hartman,[231] in a description of renal damage associated with extensive burns, reported changes in the tubules (particularly in the proximal convoluted tubules, less frequently in the distal convoluted tubules), the blood vessels, the glomeruli, and the interstitial tissue

Bell and Knutson,[26] in a study of 84 patients who were preterminal and had azotemia (urea nitrogen 50 or more) from a variety of causes, found histologic changes in the kidney in only 20 In these 20, mild to severe hydropic degeneration of the *proximal* convoluted tubules was observed There was no correlation between the histologic findings and the level of the blood urea nitrogen, or the severity of the oliguria

Acute Renal Insufficiency without Apparent Histologic Changes

Acute renal insufficiency may occur without gross or histologic evidence of kidney damage as in the cases of 'low salt syndrome' reported by Schroeder[333] or in the preterminal cases of Bell and Knutson [26]

Failure of tubular function often develops before pathologic changes become apparent Mallory[220] found no visible changes until eighteen hours after the onset of shock and oliguria in wounded soldiers, and concluded that at this stage, "The initial renal insufficiency is, therefore functional rather than anatomical in basis" There appears to be no correlation between the degree of kidney dysfunction and the histologic picture However, in renal insufficiency resulting from hemorrhage, shock, or nephrotoxic damage to the tubules a more constant morphological pattern is discernible

Microdissection of Individual Nephrons

A major contribution toward an understanding of the pathology of acute renal insufficiency was made by Oliver and his group[275, 276] by the use of microdissection technique They demonstrated two general types of morphologic change confined to the tubules which could be correlated with two main etiologic factors, shock and nephrotoxins

The "Ischemuric Kidney"

In the first group, kidney damage is due primarily to shock (ischemuric episode), and the insult is considered predominantly circulatory Here the histologic picture is characterized by "disruptive tubular damage or 'tubulorrhexis" These lesions occur at *random areas* of the nephron and in *random nephrons* In Oliver's[275] dissections

> As one follows the course of the intact tubules, quite suddenly, a place is found where the basement membrane is broken, frayed or disintegrated, and the epithelial lining disrupted and necrotic The result is a solution of continuity which may include only a part of the wall of the tubule or which completely interrupts its course so that the fragmented remnants lie between a still intact and well preserved proximal portion and its distal prolongation The lumen thus lies open to the intertubular, interstitial tissue and its capillaries and veins

Oliver[275, 276] stated that the histologic picture will vary in accordance with the extent of damage, the presence or absence of casts in the lumen, and the possible reaction of the interstitial tissues in the vicinity of the rupture Evidence of reparative processes may be visible even in the most severely damaged segments of the nephrons Thus, disruption of the basement membrane of the tubule is the dominant and characteristic pathologic development in nephrons damaged as a result of shock (fig 1)

The "Nephrotoxic Kidney"

In the second group of cases described by Oliver,[275, 276] insult to the kidney results from the presence of nephrotoxic substances which are (in his cases) mercuric chloride, potassium chlorate, diethylene glycol, carbon tetrachloride, sulfonamides, and mushroom poisoning (fig 2)

With this type of renal injury, necrosis of the tubular epithelium is found evenly distributed throughout all the nephrons with predominance at the proximal convolutions A characteristic feature is the intact basement membrane despite severe damage to the renal tubular epithelium In addition the tubulorrhexia of the 'shock kidney is scattered at random throughout the nephrons



Figure 1 Complete proximal convolution from acute tubular necrosis following fatal burns Death on ninth day In its first loop (right) the tubule is fairly well preserved from there on extensive tubulorrhexic damage (OLIVER J Correlations of structure and function and mechanism of recovery in acute tubular necrosis Am J Med 15 535–557 1953)

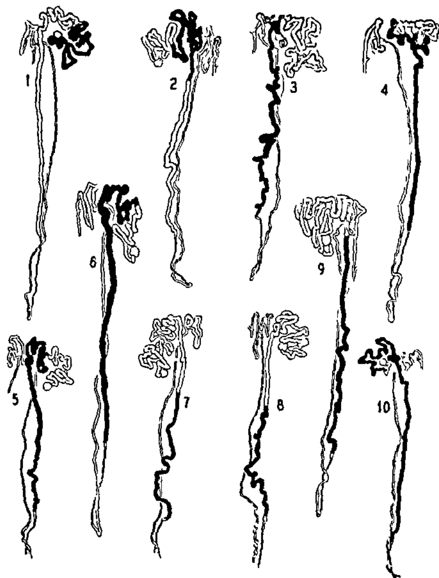


Figure 2 Localization of nephrotoxic damage in the proximal convolution in various forms of poisoning 1) Potassium bichromate 2) uranyl nitrate 3) corrosive sublimate 4) sodium potassium tartrate 5) potassium chlorate 6) diethylene glycol 7) carbon tetrachloride 8) mushroom poisoning 9) serine 10) sulfonamides The necrotizing effects of moderate doses in shown by black areas with large doses the area of localization tends to spread and there is the further complication of an ischemuric episode with the development of disruptive tubular lesions Magnification 20× (Oliver J Mac Dowell M and Tracy A The pathogenesis of acute renal failure associated with traumatic and toxic injury Renal ischemia nephrotoxic damage and the ischemuric episode J Clin Invest 30 1307–1440 1951)

TABLE 1

Correlations of Structure and Function in Acute Renal Failure (Acute Tubular Necrosis)

Functional Disturbances	Structural Changes
The Oliguric Phase	
1 Reduction in renal blood flow and glomerular filtration	1 Glomerular capillaries empty with tufts collapsed but intact
2 Albuminuria	2 Protein in capsular space
3 Hemoglobinuria	3 Heme pigments in capsular space and tubule lumens, heme casts
4 Loss of proximal tubule function, inability to concentrate urea and creatinine to conserve electrolyte and to extract PAH	4 Beginning tubular damage—lack of proximal absorption of heme pigments, increasing to tubulorrhexic and nephrotoxic necrosis
5 Relative maintenance of glucose Tm	5 Structural integrity of first one-third proximal convolution
6 Persistence of reduced RBF after initial insult	6 Tubular leakage interstitial edema and reaction and increased intrarenal tension
The Early Diuretic Phase (Occurrence of Diuresis as Result of Reparative Phenomena)	
1 Onset of diuresis as a result of absorption of interstitial edema, increasing blood flow and filtration with continuing depression of tubular absorption of water	1 Distended glomerular capillaries and normal appearing tufts, persisting tubular damage, nephrotoxic and tubulorrhexic, with especial involvement of proximal convolution
2 Persisting evidence of abolition of proximal tubule function (lack of ability to concentrate urea in urine, inability to conserve electrolyte or extract PAH)	2 Extensive atypical regeneration of renal epithelium—absence of mitochondria and consequent reduced enzymatic content of new renal epithelium, excess epithelial proliferation and tubular dilatation
The Late Diuretic Phase	
1 Gradual recovery over weeks or months of tubular functional ability with possible eventual clinical recovery	1 Slowly progressive maturation of regenerated tubular epithelium with ultimate reconstitution of original structures including mitochondrial organelles with their enzymatic content
2 Renal function after clinical recovery adequate but remaining below lower limits of normal	2 Loss of nephrons from irreparable tubulorrhexic damage and associated hypertrophy and hyperplasia of others

OLIVER, J Correlations of structure and function and mechanism of recovery in acute tubular necrosis Am J Med, 15. 535, 1953

Interstitial Changes

In Oliver's study,[275, 276] reaction of the interstitial tissue varies from a complete absence of damage when the integrity of the tubules is retained, to alterations characterized by firmly attached masses of connective tissue fibers which surround the damaged tubules or granulation tissue and proliferation of capillaries which sometimes grow into the disrupted lumen

The most striking histologic feature of kidneys injured by nephrotoxins is the interstitial edema and infiltration of leukocytes predominantly at the site of disrupted tubules Finally, it should be noted that in overwhelming renal intoxication from any cause, the impairment of circulation can be severe enough to cause ischemuric episodes and histologic changes identical to those resulting from shock (table 1)

Reparative Processes

A brief description of reparative processes is necessary to complete the pathologic picture Reparative changes begin soon after reaction to the original insult Restoration of the nephron as a functioning unit depends largely upon the re establishment of continuity in the lumen The probability of complete functional restoration of the nephron decreases in proportion to the intensity of damage It is likely that disruption of the basement membrane of the tubule precludes the return of nephron function When the *basement membrane remains intact the possibility of tubular epithelial cell replacement and re establishment of continuity in the lumen are enhanced* *Therefore, the restoration of renal function depends to a large extent upon the degree of tubulorrhexis, which in turn is affected by the intensity and duration of renal circulatory impairment* This accounts for the extreme variability of clinically demonstrable damage residual in kidneys injured by shock or nephrotoxins

Renal Lesions in Epidemic Hemorrhagic Fever

Oliver and MacDowell[277] described in considerable detail the pathologic alterations of the kidney in epidemic hemorrhagic fever

In cases from the Korean theater, histologic changes were correlated with the clinical course Although the disturbances of renal function in epidemic hemorrhagic fever are largely the result of circulatory changes and anoxia, the toxins of the etiologic agent are probably also a factor in the pathogenesis The symptomatology and associated pathologic changes were considered in the four characteristic phases of the disease No study has thus far been made of renal tissue obtained by biopsy from patients surviving epidemic hemorrhagic fever, therefore, present knowledge is based entirely upon autopsy study

Febrile Phase

Clearance studies in the febrile phase[117, 872] showed a normal or increased renal blood flow compatible with the characteristic dilatation of the peripheral vascular bed This is followed by increased permeability of the capillaries and venules

[277] There [illegible]

on the tubules of nephrons that by chance pass through it, but no structural evidence of general cellular damage in any of the tubules The tubular passages are clear there are few casts

Thus, in the first stage no serious structural alterations of the nephron could be demonstrated either in the histologic sections or in the elaborate nephron dissections

Further capillary permeability and dilatation of the small vessels resulted in shock and hypotension, augmented in some patients by hemorrhage into the anterior pituitary and right auricular musculature

Hypotensive Phase

These events inaugurate the second or hypotensive phase during which the renal blood flow is decreased and the hematocrit is elevated without a corresponding elevation in total protein, resulting in a clinical state resembling surgical shock The histologic appearance of the kidney in this stage of epidemic hemorrhagic fever dif

fers from that observed in surgical shock in that engorgement of the medullary region is more intense in epidemic hemorrhagic fever

[277] the contents of the subcortical capillaries become an almost solid mass of entrapped red blood cells Plasma which has escaped through the abnormally permeable vessel walls is found in areas of intertubular edema which may extend into the medulla and, by means of medullary rays, into the cortex

These physiologic and structural changes are associated with a rise in blood urea nitrogen despite the absence of oliguria which is characteristic of the third phase

Oliguric Phase

Before the third or oliguric phase, a transition period often occurs during which fatal shock may obtain despite the return of blood to the vascular compartment as indicated by a decrease in the hematocrit and an increase in plasma volume Examination of the kidneys in fatalities during the Korean war disclosed gross hemorrhage in the congested subcortical zone Histologic sections of this zone showed intensive intertubular hemorrhage in contrast to the previous stage wherein this congestion was due to greatly dilated but intact intertubular vessels There is, therefore, as in all examples of acute tubular necrosis and renal failure, no preferential damage to the 'lower nephron but rather the reverse [277]

The intense congestion, dilatation, and ultimate hemorrhagic rupture of the intertubular vessels of the subcortical zone extend into the cortex and deep into the medulla, and compress portions of the tubules resulting in obstructive dilatation of the proximal segments Random fragmentation of the tubules with disruption of the basement membrane similar to the tubulorrhexia of acute renal failure was also observed in some sections Many of the epithelial cells in the proximal convolution were filled with hyaline droplets, and in other subcortical areas the tubular cells were distorted and destroyed by compression of the intertubular hemor

rhage These alterations culminate in diminution of urine formation which characterizes this phase

The characteristic pathologic alterations and resultant functional disturbances now reach the zenith of destruction, and the nephrons are probably damaged beyond restoration The typical histologic change, therefore, is obstructive dilatation of the proximal and distal convolution, a sort of "intranephron hydronephrosis" refluxing back into the glomerulus resulting in dilatation of Bowman's space The stasis dilatation of the intertubular vessels and the interstitial hemorrhage thus completely obliterate the circulation of blood in the nephron

Diuretic Phase

As in all examples of acute renal insufficiency resulting from toxic injury, the tubule is damaged throughout its entire length from the glomerulus to the collecting tubule The damage is most intense at the proximal convolution during this stage Renal tissue shows considerable evidence of resolution and regeneration, and repair of the nephrons is apparent In some instances, congestive hemorrhage becomes severe and extends from the subcortical zone to the papillae Fragments of disrupted and denuded tubules show mitotic figures indicative of abortive attempts at tubular regeneration Tissue obtained from a patient who died on the fifth day of diuresis had resolution of the hemorrhage and replacement fibrosis

Casts

In all types of acute renal insufficiency associated with the excretion of blood pigments,[63, 73, 220] hematogenous casts first appear in the ascending limb of the distal tubule and become numerous in the distal collecting tubules In the presence of proteinuria, casts of albumin and globulin may form in the same segments Heme casts are present in transfusion reactions and other forms of intravascular hemolysis, shock, and crushed muscles (myoglobin)[63]

The relation of the cast[73] to the lesion in the lower nephron has created much speculation The localization of morphologic changes

to this latter segment has been attributed to a decubitus reaction to casts and resulting foreign body like response Casts, however, are not present in a sufficient number of nephrons to account for the oliguria by blockage In one study, casts were found in only twenty per cent of *the nephrons examined in a kidney damaged by shock*[235]

Changes in the Collecting Tubules

In acute renal insufficiency, the epithelium of the collecting tubules is usually normal but can be intensely necrotic, and occasional *regenerative changes involving this segment have been reported* This segment of the nephron is the most frequent site of pigment casts Using microdissection technique, Darmady[74] observed atrophy of the collecting tubules in renal tissue obtained from several patients who died during the diuretic phase of acute renal insufficiency

Renal Biopsy

Considerable progress in the development of renal biopsy techniques has been made[13, 56, 132, 165, 17?, 20?, 259, 260, 298] A minor number of untoward reactions have been reported from biopsy procedures,[298] but fatalities have been extremely rare Sheldon and his associates[343] performed renal biopsies on two anuric patients, and attributed blood clot formation in the pelvis to the procedure

Iverson and Brun[165] reasoned that renal biopsy is of greatest value in the study of those mild renal disorders which rarely come to autopsy, or in the early stages of severe, acute renal insufficiency A biopsy performed on the eighth day of oliguria disclosed normal glomeruli in a patient who developed acute renal insufficiency following afebrile abortion However, ' In Henle s loops and in particular, in the distal convoluted tubules, numerous heme casts are seen, often containing lymphocytes leukocytes, and remnants of nuclei there is no necrosis of the tubular cells anywhere "[165] *The authors observed that the changes demonstrated are conspicuously insignificant considering the state of suspended renal function* In a report of seventeen renal biopsies performed on twelve

patients anuric from two to sixty two days the following changes were observed [165] The glomeruli were normal the proximal tubules had a low flattened epithelium and were dilated in some cases the epithelium showing hydropic changes in some areas and in the tubular epithelium as a whole both degenerative and regenerative processes were present often side by side Hemoglobin stained casts were seen in the distal tubules Henle s loops and the collecting tubules The degenerative change in the tubular cells was also and perhaps chiefly localized to the proximal tubules

Thus Iverson and Brun[165] concluded that the term lower nephron nephrosis is inaccurate because histologic findings on biopsy specimen prove that the injury is not confined to the lower segment alone but is also present in the proximal tubules and therefore suggested acute tubulo interstitial nephritis as a more appropriate designation

Govan and MacGillivray[133] classified some of their cases as upper nephron nephrosis since most of the changes in three of these cases occurred in this portion

Berman *et al* [23] studied two surviving patients with acute renal insufficiency from ethylene glycol poisoning Needle biopsy of the kidney was performed on the fourteenth day of illness in one patient demonstrating the characteristic histologic picture of this condition They[28] described widespread necrosis of the renal tubules with apparent preservation of the basement membrane and precipitation of calcium oxalate crystals within the tubular lumina The presence of these crystals suggests that oxalic acid a metabolic product of diethylene glycol is the nephrotoxic agent Similar lesions have been produced in experimental animals with oxalic poisoning

Brun and Munck[43] investigated a total of thirty three patients with acute renal insufficiency following shock from various causes and performed twenty renal biopsy examinations in seventeen of these patients In general their studies corroborated previous observations They too were especially impressed with the phenomenon of moderate morphological changes in the presence of complete functional breakdown

The Pathophysiology (Pathogenesis) of Urinary Suppression in Acute Renal Insufficiency

Although oliguria and anuria are considered the cardinal clinical manifestations of acute renal insufficiency, they are not invariably present An occasional case may present severe azotemia notwithstanding adequate urine formation It is evident, therefore, that no one factor can be solely implicated in all cases of acute renal insufficiency We concur with Oliver[276] that there is no single cause but a constellation of causes acting in summation and resulting in suppression of urine These various and much disputed pathophysiologic alterations which produce suppression of urine are considered in this chapter under the following classifications 1) the effects of shock on renal circulation and glomerular filtration, 2) the effects of shock and nephrotoxins on tubular function and the non specific total reabsorption of glomerular filtrate, 3) tubular obstruction by casts 4) increased intrarenal pressure, 5) Trueta[381] shunt, 6) reflex anuria, and 7) antidiuretic hormone effects

The Effects of Shock on Renal Circulation

Primary and Secondary Shock

The clear-cut separation and the basic mechanism of the various types of shock still remain to be clarified despite intensive and prolonged study by clinicians and research teams In a sense, 'shock' constitutes a spectrum of hypotensive states ranging from mild, rapidly reversible neurogenic shock to secondary irreversible, fatal wound shock and includes such diverse conditions as bacteremic shock, anaphylactic shock, and hemorrhagic shock At the beginning of the spectrum are the "shock like" hypotensive states which

are largely neurogenic (vasovagal), appearing immediately after emotional or physical trauma

It is well to remember that hypotension per se is an equivocal term[318] *The symptoms often depend upon the usual blood pressure level of the patient* Thus, the symptoms of shock may appear in a normotensive individual when the pressure falls below 80/50, whereas in a hypertensive patient, shock like symptoms may occur when the pressure falls, for example, from 210/110 to 110/70

Our primary concern is secondary shock, a state of peripheral vascular collapse which follows immediately or several hours after a number of conditions, i e, trauma (wounds, burns, fractures crush injuries, hemorrhage), infarction (myocardial, pulmonary, mesenteric, cerebral), anaphylaxis, bacteremia, toxemia, acute ad renal insufficiency to mention only a few of the many potential causes

The state of secondary shock is characterized by an extreme fall in blood pressure, gray cyanosis of the fingertips toes, nose, and lobes of the ears, rapid shallow respirations, a fast, thready pulse, apprehensive moaning, muscular weakness, prostration, apathy, blunted sensorium, depression of body temperature, sweating in some patients and dryness of the skin in others[29]

Although the physiologic manifestations of shock, i e, decreased venous return and cardiac output, hemoconcentration increased capillary permeability, peripheral vasoconstriction, sludging of blood, tissue anoxia, and increased blood ammonium concentrations, have been thoroughly recorded, the basic mechanisms producing these alterations remain to be clarified

A vast amount of clinical and experimental data was accumulated during and following World Wars I and II and the Korean conflict concerning the mechanism of wound shock and hemorrhagic shock

Several theories have been advanced to explain the mechanisms of the various types of shock The toxic theory holds that a histaminic or histamine like substance is released into the circulation from the site of injury This theory is weakened by the fact that such a substance has not yet been isolated from ex

perimentally traumatized tissue which will produce shock in a normal animal

On occasion the extreme hypotension of shock has resisted all treatment including blood transfusions and plasma and has resulted in death The mechanism of this irreversible form of shock is not clear The most acceptable explanation to date has been offered by Shorr *et al*[345] as a release of a vasodepressor substance VDM Crowell and Read[80] have attributed this irreversibility of shock to the formation of thrombi within the systemic capillaries resulting from increased coagulability of the blood The response of this overwhelming form of shock to the administration of L norepinephrine and pharmacologically related substances is a notable therapeutic triumph in that many who would formerly have died now survive with this treatment

Bacteremic Shock

Bacteremic shock is a not uncommon yet frequently overlooked cause of vascular collapse[149] and acute renal insufficiency[230] The usual manifestations of shock may be absent or obscured by the symptoms of fulminant septicemia and the clinician may be alerted to its presence only by detection of low blood pressure Bacteremic shock is caused most frequently by those antibiotic resistant gram negative infections which often terminate in death[140] The precise mechanism of bacteremic shock is not known but recent studies indicate that the harm is mediated by endotoxins acting directly on the vascular system producing peripheral vasodilation[37]

Shock and Glomerular Filtration

A vast amount of investigation has been devoted to the physiologic differences between the various types of shock It is our impression that whatever the cause and mechanism of secondary shock its effect on the kidney is the same

Van Slyke[384] has shown experimentally that oliguria occurs during both primary and secondary shock *The oliguria of the first*

muscle For example, adenosine triphosphate, a nephrotoxic sub stance, has been isolated from ischemic muscle[31, 366] These sub stances may injure the kidney as they are excreted Of great clinical importance is the fact that *some degree of renal ischemia accom panies all states of circulatory failure and severe systemic reac tions*[353]

CASE REPORT

L M, a thirty two year old Mexican male, entered Mount Sinai Hospital on May 15, 1956, for surgical treatment of an acute suppura tive appendicitis Immediately postoperatively, his temperature rose to 105 F, and symptoms of shock were observed The blood pressure was 60/40, and the pulse rate 120 Norepinephrine was administered by slow intravenous drip, but the shock like state persisted for twenty *four hours A portable roentgenogram disclosed elevation of the right* diaphragm and pneumonitis of the right lower lobe which were at tributed to atelectasis and a right phrenicoexeresis performed six years previously for pulmonary tuberculosis Because of the persistence of shock despite antibiotics, oxygen blood transfusions and norepineph

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second postoperative day, a persistent oliguria was noted ot between

tern remained unchanged The blood urea nitrogen rose from a normal

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the white

On the ninth day of oliguria the diuretic phase began with a urinary output of 2700 cc During the oliguric period, fluids were limited to 1000 cc of 10 per cent glucose plus the volume obtained by gastric suction The patient expired on the tenth postoperative day, May 25, 1956

Autopsy disclosed bilateral pulmonary atelectasis due to obstruction

by mucoid plugs Healed tuberculosis of the right upper lobe was evident Both kidneys were enlarged, and cut section showed a gray, reddish cortex and a dark red medulla with sharp demarcation Microscopic examination of the renal tissue disclosed necrosis of the distal tubules heme casts and interstitial inflammatory reactions surround ing these casts

Comment This is a typical example of necrosis of the distal tubules and rupture of the basement membrane described by Oliver as the ischemuric kidney The anoxic damage to the tubules resulted from the renal ischemia of shock and the im paired oxygenation of blood which resulted from the massive atelectasis The severe overwhelming infection, prolonged shock, and anoxia were of such intensity and duration as to produce renal damage beyond reversibility

Hemoconcentration, Blood Viscosity, and Sludging

Hemoconcentration increased blood viscosity and sludging resulting from shock contribute materially to the impairment of glomerular filtration Hemoconcentration increases blood vis cosity reduces the rate of renal blood flow, increases the oncotic pressure in the glomerular capillaries, and finally inhibits glo merular filtration

VEM and VDM of Shorr et al[345]

Shorr Zweifach Furchgott, and Baez[345] demonstrated a hepato-renal mechanism for maintaining circulatory homeostasis They isolated two substances from the blood of shocked' animals The first, VEM, is produced by the kidney and has a *pressor* effect on the meta arterioles and precapillary sphincters The second, VDM, produced chiefly by the liver, [illegible] to ferratin and has a *depressor* effect on the meta [illegible] ecapillary sphincters Both of these [illegible] r anerobic conditions and are inactivated [illegible] under aerobic conditions

Thus homeostatic mechanisms producing anoxia of the liver and kidney during shock may contribute to the impairment of renal function

Short *et al*[345] demonstrated that this homeostatic mechanism is operative in dogs and rabbits during hemorrhagic and tourniquet shock They observed two phases referable to VEM and VDM activity In the first phase which is compensatory and reversible an excess of VEM is produced by the kidney In the second phase which is irreversible VDM is predominant probably due to an impairment of the mechanism inactivating VDM in the liver

The Effects of Shock and Nephrotoxins on Tubular Function

Non Specific Total Reabsorption of Glomerular Filtrate

Non specific total reabsorption of glomerular filtrate resulting from tubular paralysis has been described as the cause of oliguria [75] By this mechanism the shocked tubules lose their selective and specific reabsorptive ability and all or most of the glomerular filtrate[384] is reabsorbed thereby producing anuria or oliguria Sirota[349] concluded that the oliguria is due mainly to a back diffusion of the glomerular filtrate across the damaged tubular wall so that the organism urinates into the kidney instead of the bladder The existence of such a mechanism is confirmed by Richards[304] who studied frog nephrons poisoned with bichloride of mercury He was able to visualize directly the glomerular filtrate in the tubular lumen and the subsequent disappearance of the filtrate *through the damaged* tubular cells Oliver[275 276] subscribed to this concept and set forth the following sequence of events resulting from tubular injury a) In the early stages there may be a short period of reduced reabsorption of water by the tubule to counteract the reduced filtration b) As renal ischemia produces more tubular damage there may be a gross pouring of tubular fluid in toto through holes in disrupted tubules at every level of the nephron c) Leakage of tubular fluid into the interstitial

tissue results in interstitial edema with increased intrarenal pressure and compression of the tubules and their thin walled afferent capillaries all leading to further renal ischemia and reduced glomerular filtration

However it should be noted that a contrary opinion is held by Smith[3 3] who has stated that the evidence for back diffusion of water through the impaired tubules is rather meager and is more of a gratuitous inference than an established fact

Tubular Obstruction by Casts

Tubular obstruction by casts was once believed a major factor in the decrease of urine flow According to Smith[353] even before anoxic injury of the distal tubule occurs an almost complete reabsorption of sodium and water effects a maximally concentrated urine favoring the precipitation of proteins (cast formation) in the distal segment and collecting tubules Smith[353] concludes however that protracted anoxia of the renal parenchyma without cast formation can lead to irreversible tubular injury Oliver[275, 276] believes that casts found in the urine are formed in the collecting tubules from which they are easily expelled and even casts formed more proximally are not necessarily obstructive Histologic examinations of the kidney in shock have shown casts in approximately twenty per cent of the tubules[255] Obstruction of this relatively small number of tubules cannot possibly account for the presence of oliguria even to a moderate degree and certainly is not responsible for total anuria

Increased Intrarenal Pressure

Increased intrarenal pressure has been suggested as the prime mechanism of oliguria on the basis of gross distention of the kidney parenchyma and the microscopic picture of interstitial edema This edema may be produced to some degree by leakage through the disrupted tubules[275, 276]

Peters[290] theorized that since the renal capsule is relatively rigid and inelastic a slight increase in the bulk of the intra

capsular renal tissues can easily cause a significant rise in intra renal pressure Thus, he reasoned that the primary cause of the oliguria or anuria is a decrease in effective filtration pressure resulting from increased intrarenal pressure which, in turn, i caused by swelling of the tubular epithelium and dilatation of the tubules He constructed an ingenious mechanical nephron to demonstrate that an increase of the intrarenal pressure by a few millimeters of mercury immediately causes oliguria or anuria and that a slight reduction promptly restores a normal urinary output

Increased intrarenal pressure, therefore, may act by 1) pres sure on the thin walled blood vessels increasing ischemia and/or 2) by compression collapse[290] of the tubule sufficient to produce obstruction to the flow of urine

Alternatively, most workers believe that increased intrarenal pressure is not a significant factor in the impairment of the forma tion or flow of urine, a view with which we concur

The Trueta Shunt

The Trueta[381] shunt, by means of which blood is diverted from the cortical glomeruli with their fine and multiple glomerular tufts to the juxtamedullary glomeruli in which there is much less filtration surface, may also be a factor in oliguria Trueta and his associates[381] demonstrated a mechanism of cortical *renal is chemia* They observed that prolonged constriction of the hind leg of a rabbit produced severe vasospasm of the arteries supply ing the cortex of the kidney, with a shunt through the juxta medullary glomeruli The arterioles of the juxtamedullary glomeruli are larger, containing fewer capillary loops, and have larger efferent arterioles, which break up into a coarse network to supply the tubules These bear the major portion of the renal circulation In some of these glomeruli the communication be tween the afferent and the efferent arterioles is, in a sense, no more than an arteriovenous connection, while the efferent ar

terioles enter almost directly into the venae rectae thereby by passing tubular tissue According to Trueta [381] this bypassing of both glomerular filtration and the nutrient vessels of the tubule by branches from the glomerular efferent arteriole is sufficient to produce a decrease in glomerular filtration and tubular damage Trueta[381] was able to produce the same effects by stimulation of the splanchnic nerve He demonstrated here a remarkable increase in the rate of renal blood flow by observing that the time required for the blood to traverse the kidney under these circumstances was halved and that the renal veins showed red streaks and pulsa tions indicating a more direct arterial communication Reports indicating improvement of the renal anoxia syndrome by splanch nic block or by spinal anesthesia may be clinical corroboration of Trueta s experimental observations

Studies by Maxwell *et al* [235] and Van Slyke[385] have not sub stantiated the existence of the Trueta mechanism[381] in all cases of human shock The existence of such a mechanism in the human is open to serious doubt and further studies are indicated

Reflex Anuria

The vascular system of the kidneys and even the tubules are under the control of complex nervous and humeral factors Re- flex impairment of urine flow in a normal kidney from disease in the contralateral kidney has been observed [189, 271, 310]

Reflex anuria from surgical manipulation of viscera other than the genitourinary tract is said to occur [16, 310, 330, 353]

These examples of reflex anuria however have not been within our experience and their existence is generally open to question

O Connor and Verney[272] reported inhibition of water diuresis in dogs subjected to emotional stress They suggested two factors operative in this mechanism 1) a rapid inhibitory factor mediated by nervous control of the renal blood vessels which was not operative after denervation of the kidney and 2) a slow inhibi tion of urine formation due to an increased release of antidiuretic hormone

Sirota and Narins[350] reported three cases in which intense oliguria and azotemia followed uncomplicated cystoscopic ureteral manipulation and retrograde pyelography Repeated cystoscopy disclosed that this interference with urinary flow was the result of bullous edema of the ureteral orifices which they attributed to a hypersensitivity to trauma, formaldehyde (used for catheter sterilization), or the dye used for retrograde visualization *Thus, reflex anuria is a catch-all misnomer which includes iatrogenic conditions To establish the precise cause of "reflex anuria" cystoscopic examination is indicated*

Antidiuretic Hormone Effects

Brun *et al* [42] studied kidney function in human subjects during circulatory collapse from prolonged, passive erect position, and demonstrated that postsyncopal oliguria is due to an increase in the secretion of the antidiuretic hormone by the para nervosa Postsyncopal oliguria lasts from fifteen to about ninety minutes after syncope Following this brief period of oliguria, urine flow returns to normal *It is of interest to note that a transfusion of blood from subjects who had just collapsed with postsyncopal oliguria, into water loaded subjects, caused a distinct decrease of urine flow in the latter*

The increased urinary chloride concentration and the increased rate of chloride excretion effected by this form of syncope correspond to the pattern of changes observed after administration of posterior pituitary extract Although these experiments indicate that oliguria is produced by antidiuretic hormone, the precise mechanism controlling the release of antidiuretic hormone remains to be established *It is possible that such a mechanism may be evoked by hypotension and other homeostatic disturbances resulting from shock*

Darmady[74] has advanced anatomic evidence suggesting that the site of action of the antidiuretic hormone in acute renal insufficiency is predominantly the collecting tubules and to a lesser degree the distal tubules

The classical studies of Verney[387] concerning the control of antidiuretic hormone release stimulated a tremendous amount of research [46] but much remains to be learned about the relation of osmotic and volume alterations to antidiuretic hormone release

3

Diagnosis of Acute Renal Insufficiency

Definition of Acute Renal Insufficiency

Acute renal insufficiency has been described[370] as a spectrum of disturbances which merges in one direction with functional renal disorders (acute disturbances of water and electrolyte balance tran sient urinary suppression associated with shock of short duration) and in the other direction with renal insufficiency associated with liver disease (hepato-renal syndrome) complications of pregnancy and severe infection

Merrill[246 370] considers renal insufficiency and renal failure as separate and distinct entities defining renal insufficiency as a la tent dysfunction which becomes apparent only with abnormal re sults of renal function tests and/or when unusual excretory de mands are made and renal failure as kidney function impaired to the degree that the normal excretory and metabolic demands can not be met To the contrary we believe that renal insufficiency and renal failure are synonymous Therefore in this volume the term acute renal insufficiency in the absence of demonstrable obstruction of urine flow designates 1) a sudden reduction of urine flow be low 400 cc for twenty four hours 2) acute symptomatic and/or bio-chemical manifestations of deranged renal function which are po-tentially reversible

We do not believe that renal damage which is not symptomati cally or biochemically evident can in truth be called acute renal insufficiency It should be noted too that acute renal insufficiency must perforce occur with greater frequency when circulatory stresses or nephrotoxins are superimposed on the previously dam aged kidney which has lost its flexibility or compensatory func tion

Diagnosis of Acute Renal Insufficiency

Before proper therapy for acute renal insufficiency can be instituted the exact cause for the suppression of urine or azotemia must be determined The diagnosis of acute renal insufficiency is based primarily on the clinician s awareness of the numerous conditions with which renal insufficiency is known to be associated (table 2) It is not within the scope of this volume to review in detail all of the causes of renal insufficiency as listed in table 2 In most of these instances, the causes of acute renal insufficiency are readily apparent Our specific purpose is to discuss those instances wherein the diagnosis may be obscure None of these conditions however serious or overwhelming, should so completely absorb the clinician s attention as to cause him to overlook the presence of acute renal insufficiency, especially since improper therapy can be fatal

Acute Renal Insufficiency without Oliguria

When acute renal insufficiency results from conditions other than shock, i e, electrolyte disturbances or nephrotoxic substances the presence of an adequate urinary output may be misleading and acute renal insufficiency can then be detected only by blood urea nitrogen determinations *When acute renal insufficiency is due to nephrotoxic agents such as bichloride of mercury or carbon tetrachloride (table 2), the maximum reduction in urine flow may not be reached until several days after the onset of other symptoms of systemic intoxication*

CASE REPORT

The patient a twenty three year old white housewife entered Mount Sinai Hospital semistuporous She was transferred from another institution after seven days of absolute anuria following the ingestion of a half glass of home permanent neutralizing solution (potassium bromate) The oliguria was noted 48 hours after ingestion of the poisonous solution. The blood pressure was 90/60 temperature 98 6 F, and the pulse rate was 102 Pulmonary edema ascites, and generalized anasarca were noted—the patient had previously been given 4000 to 5000 cc.

[illegible]

TABLE 2

Causes of Potentially Reversible Renal Insufficiency (Non-obstructive)

1 Shock

Medical[121]
Myocardial infarction
Pulmonary infarction
Arterial embolization
Cerebral vascular accident
Cholemia
Hepatorenal syndrome[357]
Hypoglycemia
Surgical
Abdominal catastrophies, i e ,[330] mesenteric thrombosis, volvulus, acute pancreatitis, perforated peptic ulcer twisted ovarian cyst, intestinal obstruction, penetrating wounds, etc[32, 218]
Crush injury[62, 52, 67, 73, 230]
Extensive burns[131, 213, 221]
Hemorrhage, massive[194, 218]
Fractures
Obstetrical[53, 283, 321]
Postpartum hemorrhage
Septic abortion[47]
Placenta previa
Abruptio placenta
Toxemia (eclampsia)[270]
Uterine rupture

2 Water and Electrolyte Disturbances

Acidosis
Sodium depletion[73, 227, 322]
Potassium depletion[90, 99, 202, 314, 412]
Fistula
Gastrointestinal intubation
Ketosis (starvation and diabetic)[131, 361]
Diarrhea[314, 324]
Chloride acidosis (ammonium chloride, calcium chloride intoxication)[348]
Respiratory acidosis
Alkalosis
Vomiting (chloride depletion)
Pancreatic fistula
Excessive ingestion (alkalies)[49]
Water Depletion
Water deprivation[227]
Solute diuresis (hypertonic glucose solutions)
Mercurial diuresis

TABLE 2—*Continued*

3 Nephrotoxins

- Copper sulfate[321]
- Carbon tetrachloride[116, 349]
- Heavy metals (mercury, thallium, selenium, uranium, bismuth, etc.)[29, 169, 171, 307, 308]
- Sulfonamides[87, 314]
- Phosphorus[130]
- Chloroform[130]
- Venoms[412]
- Acetazolamide (Diamox)[136, 287]
- Neomycin[246]
- DDT
- Diethylene glycol
- Djenkol Bean[301]
- Mushroom
- Phenourone
- Toluene[60]
- Potassium chlorate
- Poison oak[416]

4 *Intravascular Hemolysis*[412]

- Incompatible transfusions[361, 388]
- Accidental infusion of distilled water[65]
- Transurethral resection—water irrigation[190]
- Fulminant malaria (Blackwater Fever)[392, 406]
- Quinine abortifacient[201, 223, 224, 376]
- Septicemia—Clostridium welchii, Streptococcus pyogenes[332]
- Chemical agents—methyl chloride, coal tar products, etc[143, 173, 410]
- Fava beans[313]
- Paroxysmal nocturnal hemoglobinuria[141]
- Paroxysmal cold hemoglobinuria[412]
- Oroya fever (Carrion's disease)[308, 397]

5 Infections

- Epidemic Hemorrhagic Fever[81, 277]
- Septicemia[140, 242]
- Acute pyelonephritis[79, 80]
- Overwhelming pneumonia
- Pseudo uremia[242]
- Waterhouse Friderichsen syndrome
- Meningococcemia
- Severe respiratory infections[381]
- Tuberculous meningitis[399]

TABLE 2—*Concluded*

6 Central Nervous System Conditions

- Cerebral vascular accident[121]
- Acute diabetes insipidus[298]
- Tumors about the third ventricle and hypothalamus[290]
- Following "brain" surgery[190]
- Ligation of cerebral arteries[216]
- Ruptured cerebral aneurysm
- Neurogenic hypernatremia and hyperchloremia[84, 271]

7 Metabolic Disturbances

- Hyperparathyroidism[8, 17, 33]
- Nephrocalcinosis[18, 134, 138, 266]
- Boeck's sarcoid[27, 126, 190]
- Vitamin D intoxication[2, 47, 71, 300]
- Gout nephropathy[108, 252, 291]
- Addison's disease
- Thyroid crisis
- Excess protein catabolism[248]
- Excess use of androgens and estrogens[100, 158]
- Fanconi syndrome[102, 191, 236, 250]
- Renal acidosis

8 Miscellaneous

- Heat stroke and exhaustion[219]
- Electric shock
- Anaphylactic reactions
- Radiation injury[68]
- Freezing
- Reflex anuria[210, 256]

ing overhydration, the patient recovered completely and has since been perfectly well

Comment This is an example of acute renal insufficiency caused by a nephrotoxin The patient was considerably overhydrated and evidenced symptoms and signs of hydremia, but nevertheless recovered after twelve days of absolute anuria

CASE REPORT

J F, a thirty five year old white male furniture finisher, entered the West Side Veterans' Administration Hospital on March 5, 1955, be-

cause of bilateral flank pain and vomiting of nine days' duration He had been working with carbon tetrachloride in a poorly ventilated room *Each evening he drank up to four quarts of beer* No previous history of renal disease was elicited Physical examination disclosed a thin, acutely ill, lethargic patient who was slightly icteric Crude muscular tremors and a 'liver flap' were noted The blood pressure was 160/90, pulse 64, and temperature 98 F Urinalysis disclosed a specific gravity of 1 010, 4 plus albumin, and numerous red blood cells and white blood cells were present in the sediment A few fatty casts were

the chest showed a moderate degree of passive congestion The non protein nitrogen was 240 mg per 100 ml, creatinine 9 6 mg per 100 ml, serum sodium 132 mEq per liter, and serum potassium 6 5 mEq per liter During the first twenty four hours, the urinary output was only 190 cc. Five hundred cc. of 20 per cent lactose were administered by Levine tube On the second hospital day, the urinary output was 330 cc.

c

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r,

serum potassium was 7 3 mEq per liter The electrocardiogram dis

The non pro

12 6 mg per

12 6 mg per

100 ml, and the CO_2 combining power 10 7 mEq per liter Because of clinical deterioration, the patient was transferred to the Research and Educational Hospital of the University of Illinois School of Medicine for vivodialysis *After a single dialysis, the diuretic phase began*, and the patient recovered completely The entire biochemical pattern returned to normal, and the patient was dismissed

Comment The diagnosis of carbon tetrachloride intoxication was based upon the history of exposure, alcohol addiction, and the clinical picture The deleterious effects of alcoholism combined with exposure to carbon tetrachloride are well known The oliguria characteristically appeared several days after the onset of the symptoms of intoxication

Electrolyte Disturbances Producing Acute Renal Insufficiency

Disturbances of electrolyte and water balance often produce acute renal insufficiency Dehydration is usually but not invariably associated with electrolyte imbalance, and conversely, electrolyte disturbances are rarely observed without dehydration Two types of dehydration have been described 1) pure water depletion, and 2) salt depletion Marriott[227] has termed these primary and secondary dehydration Except for unusual circumstances of water deprivation, dehydration is due to salt depletion or occasionally a combination of salt and water depletion It is difficult and impractical to determine which of these two types of dehydration is dominant in the production of the acute renal insufficiency

CASE REPORT

The patient, a forty two year old negro male, entered the Cook County Hospital on January 18, 1949, because of generalized edema, dyspnea, and orthopnea resulting from syphilitic aortic insufficiency The physical examination disclosed advanced congestive heart failure and generalized anasarca The blood pressure was 140/60, pulse 90 and regular, and respirations 26 The typical diastolic, blowing murmur of aortic insufficiency was audible over Erb s point The non protein nitrogen on admission was 57 mg per 100 ml and the creatinine 1 7 mg per 100 ml Vigorous treatment for congestive heart failure was instituted i e, rapid digitalization and mercuhydrin, 1 cc. intramuscular, daily There was immediate mobilization of fluid and the edema disappeared. Five days later the patient became somnolent, nauseated, and anorexic The non protein nitrogen was now 162 mg per 100 ml, the creatinine 9 0 mg per 100 ml, and the hematocrit 41 The clinical impression was that of salt-depletion syndrome from excessive mercurial diuresis Sodium chloride was given freely by mouth and intravenous saline was administered He immediately showed considerable improvement, the hyponatremia was corrected and the azotemia rapidly cleared He was discharged from the hospital on February 22, 1949, well compensated and clinically improved (table 3)

Comment This patient fits into the category of ' low salt syndrome as first described by Schroeder[333] The mild renal insufficiency evidenced by a slight elevation of the non protein nitrogen

TABLE 3

Date	NPN	Urea	Creatin ne	Hematocrit	Chlorid
1/18/49	57		1 7		
1/27/49	133		8 7		
1/28/49	162	104	9 0	41	
1/31/49	178	139	7 5	34	106
2/ 1/49	156	110	4 7	34	
2/ 2/49	108	88	2 8	22	
2/ 4/49	75	55	2 1	27	
2/ 7/49	52	33	2 1	33	108
2/ 9/49	53		2 4	33	
2/14/49	46	30	1 7	34	
2/16/49	61	41	2 7	33	
2/21/49	45	28	1 8	32	117

on admission was exaggerated by sodium depletion and dehydr tion This was further corroborated by the fall in non prote nitrogen, creatinine, and hematocrit after correction of the hyp natremia

CASE REPORT

A J , a thirty seven year old Mexican male, entered Mount Sinai Hc pital on June 7, 1952, acutely ill because of weakness, dizziness, nause vomiting, and severe diarrhea of ten days' duration Two years prev ously, a tuberculous right testicle was removed He appeared extremel weak and emaciated The blood pressure was 94/60, pulse 86, respir

glucose 95 mg per 100 ml , and the blood urea nitrogen 85 8 mg pe

acidosis and dehydration Treatment with adrenal steroids and intr venous saline and glucose produced a rapid recovery Within three day the biochemical pattern, including the blood urea nitrogen, returne to normal, and the patient was discharged for outpatient managemen of chronic adrenal cortical insufficiency

Comment The acute renal insufficiency here was the result o

electrolyte depletion acidosis and dehydration and developed despite a more than adequate urinary output Correction of ad renal cortical insufficiency and restoration of water and electrolyte balance resulted in rapid clinical improvement and reduction of the blood urea nitrogen to normal

Addison s disease in crisis commonly is associated with acute renal insufficiency Several mechanisms probably combine to produce this effect sodium depletion dehydration and shock probably are dominant (Chapter 2) Dehydration is further augmented by vomiting and diarrhea Because of the dramatic improvement of this crisis with the proper administration of electrolytes and steroids it may be classified as a reversible form of acute renal in sufficiency

Sodium Ion Disturbance

Sodium depletion is invariably associated with loss of water and shrinkage of the extracellular fluid compartment Significantly more sodium than water is lost a mechanism which protects the blood volume[266] at the expense of tonicity in order to delay peripheral vascular collapse Thus in hyponatremia there is both a relative and absolute decrease in sodium Also sodium loss results in acidosis compensated or uncompensated as evidenced by a fall in both CO_2 content and CO_2 combining power Concomitant loss of both sodium and chloride ions results in intense dehydra tion and hypoelectrolemia

In simple water deprivation there may be an actual rise in the serum sodium level combined with intracellular desiccation and intense thirst[287, 288] This increment in sodium level is known as the reaction of dehydration[289]

CASE REPORT

The patient a thirty-eight year old negro housewife entere l Cook County Hospital on January 15 1949 in a deep comatose state The respiratory rate was 12 and Kussmaul in type The blood pressure was 130/80 the temperature 102 F and the pulse 110 She appeared in tensely dehydrated Examination of the urine disclosed a specific grav

ity of 1 024 and sugar and acetone in large amounts The diagnosis was

therapy with insulin and intravenous saline resulted in a rapid recovery within twenty four hours The azotemia subsided completely and the hematocrit dropped to 30 The patient recovered and was discharged to return for out patient management of diabetes

Comment It is evident that acute renal insufficiency in this patient resulted from the intense dehydration and acidosis associated with diabetic coma *Diabetic acidosis is one of the few conditions in which acute renal insufficiency occurs in the presence of polyuria*

CASE REPORT

R F, a forty-one year old negro male laborer and chronic alcoholic addict for many years, entered the West Side Veterans' Administration Hospital on July 26, 1956, with the symptoms and signs of fulminant pneumonia He appeared acutely ill dyspneic, tremulous, and mildly confused Temperature was 98 4 F, pulse 104, respiration 36, and blood pressure 110/80 Physical signs of extensive pulmonary consolidation were evident Symptoms of impending delirium tremens appeared and

liter After a stormy course he improved The azotemia subsided, a... the entire biochemical picture returned to normal The patient was discharged completely recovered and with no evidence of impaired renal function

Comment An overwhelming pulmonary infe... ...ined with intense dehydration in a ... malnc ...oholic addict resulted in acute ren... y ... never prominent during the ... The ... was

similar to the "pseudo-uremia" associated with bacterial toxemia as described by Meroney[242] in battle casualties

Chloride Ion Disturbance

HYPOCHLOREMIC ALKALOSIS

The state of metabolic alkalosis resulting from chloride depletion due to vomiting or gastric suction may cause an acute deterioration of renal function Metabolic alkalosis is more harmful to the kidney than a corresponding degree of metabolic acidosis Patients with preexisting renal disease are especially vulnerable to the effects of alkalosis Muscle cramps, particularly of the calf muscles, are an important practical clue to the existence of chloride depletion The biochemical pattern is one of low serum chloride, high CO_2 content, normal or high serum sodium, normal or low serum potassium levels and an alkaline pH

Nicol,[267] in a study of six patients with hypochloremic alkalosis and renal insufficiency resulting from vomiting, concluded that acute renal insufficiency in these circumstances resulted from dehydration and hemoconcentration He emphasized that the kidney may continue to produce acid urine despite intense systemic alkalemia He suggested that dehydration and hemoconcentration will impair the renal blood supply and result in tubular damage The failure of these damaged tubules to secrete alkaline radicals further aggravates the alkalemia

Perlmutter[296] also noted that hypokalemic alkalosis resulting from loss of enteric fluid or urinary loss after major surgical procedures may lead to tubular damage In these circumstances, he advises the administration of potassium ions despite oliguria to inhibit the nephrotoxic effect of hypokalemia

Fifteen cases of distinctive vacuolar tubular nephropathy were studied by Kulka and his associates[187] No correlation was observed between the signs and symptoms of kidney dysfunction and the severity of the vacuolization of the tubules Nutritional disturbances, electrolyte imbalance (ammonium chloride acidosis,

potassium deficiency), and administration of hypertonic "sugar" solutions were advanced as the possible causes of this pathophysiologic alteration

The details of the renal effects of alkalosis and potassium deficiency are covered in Chapter 9

IATROGENIC HYPERCHLOREMIC ACIDOSIS (AMMONIUM ION INTOXICATION)

In the presence of latent, impaired kidney function, the administration of large quantities of acidifying salts, such as ammonium chloride, in the treatment of heart failure, anasarca, premenstrual water retention, or cough may produce chloride ion intoxication (chloride acidosis)

Ammonium chloride is absorbed by the bowel into the portal circulation and transported to the liver where the toxic ammonium ion is converted to urea, liberating excess chloride ions Damaged tubules are unable to form sufficient ammonium cations for pairing with these chloride anions for urinary excretion, consequently, *sodium ions are displaced from bicarbonate ions Under these* circumstances, much sodium is lost in the urine as sodium chloride, and chloride acidosis results The biochemical pattern of this state is that of low CO_2 combining power and content, high serum *chloride level, normal or low serum sodium level, and an acid pH* Typical symptoms and signs of acidosis develop, i e, hyperventilation, Kussmaul breathing, lethargy, acute renal insufficiency, and eventual coma Chloride acidosis usually responds to the oral or intravenous administration of alkalies (sodium bicarbonate, 1/6 M sodium lactate solution)

Keith *et al*[174] appear to have been the first to record severe acidosis and azotemia from the administration of large quantities of ammonium chloride to patients with renal impairment Similar experiences have been reported by Sleisenger and Freedberg[352] and Sievers and Vander[346] Ammonium chloride produces these untoward effects by 1) the acidifying action of chloride ions which

cannot be excreted in excessive amounts by damaged kidneys, and 2) the toxic effect of the ammonium ions

Iatrogenic hyperchloremic acidosis and potassium deficiency have also been reported[192] in association with bilateral trans plantation of the ureters into the colon Under these circumstances, hypopotassemia augments the tubular dysfunction This defect is biochemically reversible with the administration of 1/6 M sodium lactate solution with added potassium

CASE REPORT

A.T, a twenty nine year old white, six month gravida female, was admitted to Mount Sinai Hospital on June 17, 1952, because of the gradual development of intense dyspnea Earlier in the course of her pregnancy, a severe anemia of undetermined cause was treated with blood transfusions, and three months prior to admission she was given 4 grams of ammonium chloride daily as a diuretic for the treatment of a moderate pedal edema The urinary output was always adequate and a mild albuminuria was detected. On admission, her respirations were deep and rapid (36 per minute), yet the lungs were clear to auscultation, and no cyanosis or venous engorgement was observed. The heart rate [illegible]

secondary acute renal insufficiency was considered Ringer s lactate solu [illegible]

ill with vomiting malaise, and a temperature of 101 F Arthralgia of [illegible]

26, 1952

Comment The administration of ammonium chloride over a prolonged period to a patient with impaired tubular function produced intense chloride acidosis and augmented the renal in sufficiency Correction of the acidosis reduced the *azotemia* According to DuBois [84] nitrogen mustard therapy is of distinct value in the treatment of acute renal insufficiency associated with disseminated lupus erythematosus and may promote a reversal of azotemia *Unfortunately at the time of this patient s illness* the administration of nitrogen mustard as a therapeutic measure in the renal complications of lupus erythematosus had not yet appeared in the literature

Impairment of ammonium ion metabolism is also one of the manifestations of severe hepato-cellular damage This phenomenon was first described by Kirk[177] in 1936 in association with elevation of the blood ammonia level Subsequent studies[346] corroborated the fact that the administration of ammonium chloride or ammonium containing drugs to patients with severe hepatic insufficiency can produce hepatic coma simulating uremia

Central Nervous System Lesions Associated with Acute Renal Insufficiency

Although it is known that gastrointestinal alterations diabetes insipidus and disturbances of carbohydrate metabolism may be associated with hypothalamic lesions [109] little attention has been given to the relation of central nervous system alterations to electrolyte disturbances and acute renal insufficiency

Sweet and his associates[371] were among the first to observe gastrointestinal hemorrhage hyperglycemia azotemia hyperchloremia and hypernatremia following lesions of the frontal lobe in man These authors reported this symptom complex in four patients in one of whom only the frontal lobe was involved and in three of whom the lesions appeared to involve structures in the vicinity of third ventricle Autopsies were performed in all four of these patients and histologic study of the kidneys disclosed no primary renal cause for this functional disturbance Moreover

renal failure in these cases developed notwithstanding an adequate urinary output It was the opinion of these authors that the hyper electrolemia and renal insufficiency resulting from lesions of the frontal lobe are mediated through the hypothalamus They suggested that these biochemical disturbances represent an exaggerated "alarm reaction Other acute conditions involving the central nervous system, such as tuberculous meningitis,[299] tumor,[290] hemorrhage, and abscess, have produced bizarre electrolyte disturbances probably by their effect on osmoreceptors[46] and volume receptors, through nervous connections not yet identified [64]

MacCarty and Cooper[215] reported that bilateral ligation of the anterior cerebral arteries resulted in profound electrolyte disturbances (hypernatremia, hyperchloremia, hypopotassemia, and severe azotemia [blood urea nitrogen 172 mg per 100 ml]) which could not be explained by a dehydration effect alone since the patient's urinary output was adequate and at times excessive At autopsy, the gross and histologic changes of the kidney were minimal and could not explain the azotemia

The authors[215] concluded that a disturbance of the cerebral mechanisms controlling electrolytes and water metabolism resulted in this hyperelectrolemic pattern and contributed to the death of the patient

MacCarty and Cooper[215] subsequently reported two cases with a similar electrolyte pattern One patient demonstrated this electrolyte disturbance following transfrontal craniotomy and subtotal removal of a chromophobe adenoma of the pituitary The other suffered from a cerebral vascular accident The protocols of these two cases did not contain data concerning the non protein nitrogen or blood urea nitrogen levels, and autopsies were not obtained

Luetscher and Blackman[214] reported five patients with a history of sulfonamide ingestion who developed symptoms of persistent cerebral damage, hyperelectrolemia, and renal insufficiency In two of the surviving patients, the signs of central nervous system injury continued with a slow and only temporary recovery Ulti

Comment The administration of ammonium chloride over a prolonged period to a patient with impaired tubular function produced intense chloride acidosis and augmented the renal insufficiency Correction of the acidosis reduced the azotemia According to DuBois[84] nitrogen mustard therapy is of distinct value in the treatment of acute renal insufficiency associated with disseminated lupus erythematosus and may promote a reversal of azotemia Unfortunately at the time of this patient s illness the administration of nitrogen mustard as a therapeutic measure in the renal complications of lupus erythematosus had not yet appeared in the literature

Impairment of ammonium ion metabolism is also one of the manifestations of severe hepato-cellular damage This phenomenon was first described by Kirk[177] in 1936 in association with elevation of the blood ammonia level Subsequent studies[316] corroborated the fact that the administration of ammonium chloride or ammonium containing drugs to patients with severe hepatic insufficiency can produce hepatic coma simulating uremia

Central Nervous System Lesions Associated with Acute Renal Insufficiency

Although it is known that gastrointestinal alterations diabetes insipidus and disturbances of carbohydrate metabolism may be associated with hypothalamic lesions[109] little attention has been given to the relation of central nervous system alterations to electrolyte disturbances and acute renal insufficiency

Sweet and his associates[371] were among the first to observe gastrointestinal hemorrhage hyperglycemia azotemia hyperchloremia and hypernatremia following lesions of the frontal lobe in man These authors reported this symptom complex in four patients in one of whom only the frontal lobe was involved and in three of whom the lesions appeared to involve structures in the vicinity of third ventricle Autopsies were performed in all four of these patients and histologic study of the kidneys disclosed no primary renal cause for this functional disturbance Moreover

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Acute Tubular Necrosis (Ischemuric Episode)

Acute tubular necrosis is the term applied to acute renal insufficiency due to an ischemuric episode and is the most common cause of acute renal insufficiency in pregnancy In Ober's series,[270] nine of forty nine renal fatalities of pregnancy showed pathologic evidence of acute tubular necrosis A review of the history of these nine cases disclosed episodes of circulatory collapse resulting from hemorrhage, intravascular hemolysis, or severe sepsis The pathologic and clinical manifestations of this type of acute renal insufficiency are similar to the effects of ischemuric episodes from other causes

Toxemia of Pregnancy

According to Dieckmann,[82] ' The term toxemia of pregnancy,' should be restricted to pre-eclampsia and eclampsia, which are identical except in the latter condition convulsions and/or coma occur ' Since toxemia is characterized at times by oliguria and azotemia which subside after correction of the eclamptic state, toxemia of pregnancy may be classified as a condition associated with acute reversible renal insufficiency

ETIOLOGY

The precise cause of eclampsia has eluded investigators [63 101 135] Many authorities have tenaciously adhered to the early theory of uterine ischemia notwithstanding the lack of evidence regarding the pathogenesis of this ischemia Moreover, the link between uterine ischemia and the clinical manifestations of eclampsia has not been demonstrated Traditionally, it has been held that eclampsia is due to some toxic substance or substances produced by the placenta [154] Such substances, however, have not yet been isolated from the placenta of toxemic pregnancies

Because sodium retention occurs in toxemia, aldosterone and related steroids have been implicated as the offending agents However, increased quantities of aldosterone have been isolated from the urine of many patients with sodium retention and edema

mately, necropsy disclosed areas of edema, gliosis, and hemorrhage of the brain

Allott[11] reported five autopsied cases (adults, infants, and children) in which elevations of serum sodium and chloride concentrations were associated with an almost complete absence of these ions in the urine Other electrolytes were handled normally by these patients Histologic evidence of renal disease was not sufficient to account for this electrolyte disturbance, but in those cases wherein the brain was examined postmortem, central nervous system lesions were found

Thus, patients suffering from any and all types of acute cerebral conditions should be carefully observed for electrolyte alterations and azotemia which may result from a disturbance of the osmoreceptors and volume receptors of the central nervous system Both increased and decreased serum electrolyte levels may result from central nervous system disturbances

Acute Renal Insufficiency Associated with Pregnancy

Acute renal insufficiency may complicate pregnancy under a variety of circumstances and conditions, i e, 1) acute tubular necrosis, 2) toxemia (eclampsia and preeclampsia), 3) bilateral cortical necrosis, 4) pyelonephritis, 5) pernicious vomiting of pregnancy, 6) pituitary necrosis In most instances, the renal insufficiency is reversible, as in eclampsia and acute tubular necrosis Other acute renal complications of pregnancy, however, such as bilateral cortical necrosis, are usually fatal Often the clinical picture is obscure, and a precise diagnosis of the renal catastrophe complicating pregnancy cannot be established readily The decreased urine flow may be transient, of only a few hours duration, or it may last for several days According to Ober *et al*[270] twenty to forty per cent of all cases of acute renal insufficiency are associated with complications of pregnancy They further assert that " in female patients with acute renal failure, about fifty per cent are or have been pregnant '[270]

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from other causes Moreover in true hyperaldosteronism edema as it occurs in toxemia is not usually present Consequently evidence favoring aldosterone or aldosterone like substances as the cause of toxemia is extremely tenuous [2]

The posterior pituitary hypothalamic system has also been implicated in the pathogenesis of this condition Increased amounts of antidiuretic hormone have been isolated from the urine of patients with preeclampsia [154] However since increased amounts of antidiuretic hormone are found in other edematous states the criticism applied to the aldosterone theory applies here also

PATHOLOGY

Necrotizing inflammation of the renal arterioles is occasionally observed in eclampsia but this is probably a secondary result of acute hypertension "[70]

A thickened glomerular basement membrane containing increased quantities of mucopolysaccharide is often cited as the specific lesion of eclampsia Pollack and his associates[295] studied tissue obtained by renal biopsy from ten patients with preeclampsia as evidenced by hypertension edema and/or proteinuria They refute the theory that increased quantities of mucopolysaccharide accumulate in the basement membrane They describe two distinct alterations in the glomeruli of patients with toxemia of pregnancy 1) swelling of the glomerular tufts and 2) thickening of the basement membrane They believe the former is the specific pathologic lesion of preeclampsia and the latter alteration the characteristic of the associated hypertension and nephrosclerosis In some patients both of these characteristic changes disappeared postpartum These observations and conclusions lose credence because the authors projected postpartum findings These results would be valid if the biopsies had been done during the preeclamptic state

It is apparent that a considerable difference of opinion exists concerning the precise renal lesion of toxemia We anticipate that

further study of this problem by means of renal biopsy examina tion will be illuminating [83]

COURSE

In most cases, impairment of renal function in severe toxemia is transient and reversible unless some other complication is super imposed, such as, placenta previa, postpartum hemorrhage, or other conditions associated with shock or dehydration Only mod erate azotemia is present at the height of a toxemic episode The usual cause of death in toxemia of pregnancy is cerebral edema with or without cerebral hemorrhage Since death is rarely due to acute renal insufficiency improvement of renal function has little effect on the course Previously healthy patients who recover from eclampsia rarely suffer from residual postpartum renal damage

TREATMENT

The treatment of toxemia of pregnancy is not within the ex perience of the authors It seems, however, after scanning the iterature extolling the merits of such drugs as veratrum viride, e rauwolfia extracts, and diamox, that the keystone of treatment ll appears to be prophylactic 1) proper prenatal care, i e, fre ent urinalysis for detection of proteinuria and periodic blood essure determinations, 2) early termination of the pregnancy by whatever method is indicated after consideration of the circum stances in each individual case

Acute Bilateral Cortical Necrosis

Acute bilateral cortical necrosis of the kidney is a rare, fulminant, usually fatal condition which may present with oliguria, anuria, and a rapid accumulation of nitrogenous products Although it has been reported in association with a number of diseases, it is generally considered one of the rare complications of pregnancy In a study of twenty three necropsied cases of renal cortical necro sis, Wells and his associates[401] reported that this condition comprises

twenty per cent of all cases of acute renal insufficiency According to Dieckmann's[82] review, seventy two per cent of seventy eight cases occurred during pregnancy

ETIOLOGY

Two thirds of the patients studied by Allen[10] were multiparous, and in forty per cent of the patients, there was some evidence of renal dysfunction antedating the cortical necrosis Acute bilateral cortical necrosis of the kidney may also occur in the presence of fulminant infections, such as, scarlet fever, diphtheria, tonsillitis pneumonia tuberculosis, and therapeutic malarial infection Toxic substances,[86, 123] such as, almond extract, cobra venom thyroid extract, camphor, and chemical poisons such as, diethylene glycol methol and butyl carbitol, or dioxane fumes, have also been implicated Reversible acute renal insufficiency due to acute cortical necrosis has resulted from the organic iodide used in aortography[315]

PATHOGENESIS AND PATHOLOGY

Necrosis is primarily due to prolonged and intense spasm of both the renal arterioles and venules[270] The period of vascular paralysis which follows further reduces renal blood flow, and stagnant thrombi are formed Thrombi formation invariably produces ischemic coagulation necrosis of all structures distal to the thrombi Urinary suppression then ensues within a few hours after ' utero placental apoplexy " (Sheehan and Moore[342] have classified all types of obstetric hemorrhagic complications, such as, premature separation of the placenta, abruptio placenta concealed and massive accidental hemorrhage, under the general term of "uretero placental apoplexy) Arrest of this process then depends upon relief of the primary spasm in the arterial tree before gross renal damage has occurred, i e, within the first two to three hours after the onset of obstetrical hemorrhage[342]

Ober *et al*[270] observed nephrosclerosis of the arcuate and interlobular arteries proximal to the site of thrombosis It is their in

terpretation that this nephrosclerosis is the preexisting morphological basis upon which cortical necrosis is superimposed

Identical lesions of acute bilateral cortical necrosis have been produced in experimental animals by the injection of various bacterial toxins[86] Thomas and Good[379] produced this condition in young rabbits by giving cortisone for several days prior to a single intravenous administration of endotoxin of gram negative bacilli It is conceivable that bilateral cortical necrosis may be anticipated in patients suffering from gram negative infections who have been treated with adrenal steroids

HYPOTENSION, OLIGURIA, AND ANURIA

Hypotension preceded the onset of acute renal insufficiency in fifteen of eighteen cases of renal cortical necrosis studied by Wells and his associates[401] These authors[401] emphasized the difficulty involved in differentiating this condition from other causes of acute renal insufficiency An accurate urinary output recorded in fifteen patients showed that twelve had total anuria for one or more days Fourteen of the patients passed less than 50 cc of urine daily during at least one half of the course of acute renal insufficiency

COURSE

Anuria or oliguria marks the onset of the disease Retinopathy, flank pain, and tenderness of renal distribution are characteristic Extreme febrile reactions and generalized edema have been observed

The duration of the disease varies widely according to Duff and Murray[86] Of the seventy-one patients they reviewed, fifty two died in four to twelve days Two patients died on the second day of urinary suppression, and one patient survived thirty two days of oliguria before death

Examination of the eye grounds in thirteen cases disclosed retinopathy which, in nine instances, consisted of papilledema and/or vascular retinopathy A dependent edema, followed in

some instances by generalized edema was observed in twenty eight of seventy one cases Blood pressure values during the oliguric phase showed no typical pattern except for a terminal depressio Thus the clinical course in most of the fatal cases is similar to th following total extirpation of the kidneys in experimental animal

Lauler and Schreiner[103] studied four fatal cases of renal cortic necrosis Three of these were complications of pregnancy and th fourth was a sixty nine year old male who suffered from seve trauma due to an automobile accident Although all of these pa tients eventually died the fact that three survived for more tha twenty four days suggested to the authors that with proper medica management the disease is potentially reversible and may be com patible with survival

Pyelonephritis Associated with Pregnancy

Pyelonephritis is an especially frequent complication in preg nancy and at times it is stubbornly antibiotic resistant A histor of previous episodes of pyelonephritis should serve to alert the obstetrician to the early recognition of this hazard Acute pyelo nephritis resulted in the death of eight of the forty nine fatal cases of toxemia of pregnancy reviewed by Ober and his asso ciates [270] Oliguria was reported in three of these eight cases

Pernicious Vomiting of Pregnancy

Hyperemesis gravidarium was advanced as the cause of death in four of the forty nine cases reviewed by Ober *et al* [270] Under these circumstances acute renal insufficiency undoubtedly resulted from the combined effects of dehydration and electrolyte imbalance which developed despite adequate urinary output In two cases autopsy disclosed changes similar to the tubular vacuolization of hypopotassemia (hypokalemic vacuolar nephropathy) The potas sium deficiency in these patients was probably augmented by the administration of glucose

Postpartum Necrosis of the Pituitary

Although acute necrosis of the anterior lobe of the pituitary may be due to factors such as diabetes mellitus sinus thrombosis and cerebral arteritis the most common cause is severe circulatory collapse from hemorrhage at the time of or following delivery Thus it is apparent that the cells of the anterior lobe of the pituitary are similar to the cells of the renal tubules in their vulnerability to ischemuric episode This rare complication of pregnancy has been comprehensively reviewed by Sheehan and his associates[240, 241] in several excellent monographs

Necrosis of the pituitary produces no immediately discernible manifestations but results in a fibrotic obliteration of the anterior lobe which produces the full blown clinical picture The clinical course of this condition is characterized by episodes simulating acute adrenal cortical insufficiency i e nausea vomiting slurring of speech mental confusion and coma Laboratory studies during coma revealed gross ketonuria hypochloremia and extreme hypoglycemia The non protein nitrogen and blood urea nitrogen were normal except in the pyrexial cases when the blood urea nitrogen levels rose to 120 mg per cent The coma in these patients is probably due to hypoglycemia and most patients respond to the administration of intravenous glucose A good number of these patients appear to survive many years despite these episodes of coma and they present the clinical appearance and course of Simmonds disease

Fulminant Infections Associated with Acute Renal Insufficiency

Post traumatic Pseudo Uremia

Meroney and others[161, 242] in a study of acute renal insufficiency reported uremia like symptoms and a consistently high mortality rate (50 per cent) in Korean War Casualties despite modern radical therapy i e artificial kidney dialysis They attributed these symptoms to the toxicity of bacterial infection and breakdown of

necrotic tissue In some cases, the symptoms appeared within two days following the onset of oliguria and could not be attributed to renal insufficiency Moreover, the persistence of the uremia like symptoms after dialysis and correction of the hyperpotassemia in dicated that the symptoms were due to bacterial toxicity rather than renal insufficiency Although symptomatically similar to uremia, this syndrome is distinguished by quantitative differences in blood chemistry and the chronology of the symptoms In post *traumatic pseudo uremia, the uremia like symptoms appear within* one or two days after the onset of the oliguria, whereas in true post traumatic renal insufficiency, uremic symptoms rarely appear before the fifth day It should be noted here that in most other types of acute renal insufficiency, uremic symptoms do not be come manifest until the second week of oliguria Azotemia de velops more rapidly in oliguric battle casualties than in oliguric patients in civilian life[161]

Meroney[241] deplores undue preoccupation with electrolyte, water, and nitrogen balance at the expense of prompt, thorough debridement and vigorous treatment of infection which, he be lieves, reduces the incidence of this syndrome

Epidemic Hemorrhagic Fever

In no other infectious disease, except perhaps cholera, do renal disturbances occur as frequently as they do in epidemic hemor rhagic fever The Russian and Japanese workers were the first to report the associated renal disturbances The condition is known to the Japanese as epidemic hemorrhagic fever and to the Russians as epidemic hemorrhagic nephroso nephritis, or Far Eastern hem *orrhagic fever* Considerable information was recently obtained from the study of patients in Korea and the Far East by military physicians

ETIOLOGY

The disease producing agent has not been isolated and the dis ease cannot be transmitted to an experimental animal[91] Since the

organism passes through a size N Berkefeld filter, it is probably a viral disease The disease may be transmitted to man by rodent ectoparasites, such as, fleas, mites, ticks, and chiggers The natural reservoir of hemorrhagic fever is probably several species of rodents

PATHOGENESIS

The mechanism producing renal damage in hemorrhagic fever is not known Froeb[117] made serial observations of renal hemodynamics in eight patients all of whom recovered The glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF) were serially determined by standard clearance techniques throughout all phases of the disease A general pattern was demonstrated of normal or slightly increased clearance in the late febril stage decreasing rapidly during the hypotensive phase, remaining low during the oliguric phase, and gradually returning to normal during diuresis and convalescence Early institution of L-arterenol therapy did not prevent a decrease in renal clearance, but did result in a transient increase in clearances as the arterial blood pressure was elevated from shock levels

PATHOLOGY

The pathologic alterations observed in this condition are so distinctive as to have become the final criterion for diagnosis[339] (see Chapter 1) The clinical course of the disease may be divided into four phases 1) febrile, 2) hypotensive, 3) oliguric, and 4) diuretic

CLINICAL ASPECTS

[124] Of 828 patients with epidemic hemorrhagic fever observed in Korea in 1953 all had proteinuria and a majority had some degree of renal insufficiency Hypotension with shock, hemorrhages, and central nervous system complications was common in over one half of the cases Of the forty two fatalities in this series, the majority had considerable renal insufficiency which contributed

to the mortality Shock was a common cause of death, and one third of the patients suffering shock eventually died

The diagnosis of epidemic hemorrhagic fever should be considered in anyone recently arrived from an epidemic area who demonstrates a sudden onset of chills, fever, prostration, headache, thirst, lower lumbar myalgia, and signs of facial flush, injection of palate and conjunctivae, petechiae of conjunctivae, palate, axillary folds and waistline [339]

LABORATORY FINDINGS

[118]Studies of the coagulation mechanism disclosed abnormalities in prothrombin activity clotting time, and a persistent thrombocytopenia, all of which are causally related to the observed hemorrhagic phenomenon Depression of the platelet count was the most common abnormality recorded, and levels dropped as low as 25,000 per cu mm in patients suffering severe shock The coagulation defect in epidemic hemorrhagic fever is similar to that observed in other types of acute renal insufficiency Also as in other types of acute renal insufficiency, electrolyte changes in epidemic hemorrhagic fever are unpredictable, and various abnormal patterns have been observed,[184] *i e, 1) hyponatremia with or without salt losing* nephropathy, 2) hypernatremia with or without a decrease in urine sodium excretion, 3) hyperkalemia 4) potassium deficiency with or without hypokalemia The phenomenon of hypernatremia without previous excessive sodium intake is similar to the hypernatremia and renal insufficiency associated with sulfonamide toxicity (see Chapter 4)

4

Differential Diagnosis of Acute Renal Insufficiency

The differential diagnosis of acute renal insufficiency involves a consideration of all causes of oliguria and anuria associated with azotemia Attention must also be directed to those clinical states previously mentioned in which azotemia occurs despite adequate or even increased urine flow

When medical and surgical conditions known to be associated with acute renal insufficiency are not apparent,[370] the following points favor the diagnosis of acute renal insufficiency

1) Absence of retinopathy
2) Absence of severe hypertension (retinopathy and severe hypertension suggest primary renal disease, i e , glomerulonephritis, pyelonephritis, and malignant nephrosclerosis)
3) Absence of fever, flank pain, and tenderness
4) Oliguria rather than total anuria (complete suppression of urine suggests obstruction or acute glomerulonephritis)
5) Specific gravity of the urine approaching 1 010 and a pH between 5 5 and 7 5 (in acute glomerulonephritis the urine is usually more strongly acid and the specific gravity ranges in the vicinity of 1 020)
6) Normal or slightly large kidneys as visualized by pyelograms, and absence of roentgen evidence of renal calcification
7) Absence of signs and symptoms of chronic renal insufficiency, such as chronic weight loss, muscle wasting, pallor, dusky pigmentation of the skin

In most instances of urinary suppression and azotemia, the recent history and presenting clinical state clearly point to some condition characteristically associated with potentially reversible acute renal insufficiency It has been our experience that in the absence of

such a history, renal insufficiency is usually due to some chronic irreversible renal disease The possible reversibility nevertheless must always be considered regardless of cause

CASE REPORT

S I, a nineteen year old white female student, entered Mount Sinai Hospital on June 19, 1955, complaining of blurring of vision, dizziness intense headaches, weakness, and lethargy of three months' duration She had scarlet fever at the age of twelve following which a persistent hypertension was observed She appeared chronically ill, slightly stuporous, but able to give an intelligent history The blood pressure was *220/140, pulse 72, and respirations 20 The heart was of normal size* and configuration and the lungs were clear to auscultation Ophthalmoscopic examination disclosed a bilateral, grade IV hypertensive retinopathy, i e, severe papilledema, macular stars cotton wool exudates, flame shaped hemorrhages, and extreme arteriolar spasm The hemogram revealed a red blood count of 3,190 000, hemoglobin 9 0 grams per cent, white blood count 7,400 with a normal differential distribution The total protein was 6 51 grams per 100 ml with 3 9 grams of albumin and 2 61 grams of globulin Eighty per cent of the phenol sulfonphthalein dye was retained at the end of one hour An intravenous pyelogram however, revealed kidneys of normal size and con*figuration The blood urea nitrogen was 63 8 mg per 100 ml* and the

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pressure to normal levels in the standing position and regression of the retinopathy The fundi ultimately appeared entirely normal A mild degree of azotemia persisted ranging from a blood urea nitrogen of 40 to 60 mg per 100 ml and a creatinine of 4 to 6 mg per 100 ml The anemia was controlled by transfusions of packed red cells at two to three month intervals, and her only complaint for two and one-half years was episodes of dizziness following an excessive dose of the 'blocking agent currently given (ansolysen inversene, or mecamylamine) The patient meanwhile was graduated from college and was *teaching school until one month prior to death on October 9, 1957* The cause of death was congestive heart failure and renal insufficiency Autopsy confirmed the diagnosis of chronic glomerulonephritis with

secondary hypertension producing massive hypertrophy of the heart, coronary insufficiency and congestive heart failure

Comment The patient suffered a considerable decrease in the physiologic reserve of kidney function and reached the vulnerable ascending portion of the curve (fig 3) Superimposed malignant hypertension and renal anemia produced further renal impairment and precipitated a preuremic state which was reversed for almost two and one half years Autonomic blocking agents, which are considered *hazardous* in the presence of azotemia, were used successfully in this patient *despite* azotemia Ultimately the arterial system developed resistance to the progressively larger doses of these drugs, and death resulted from the effects of hypertension on the heart

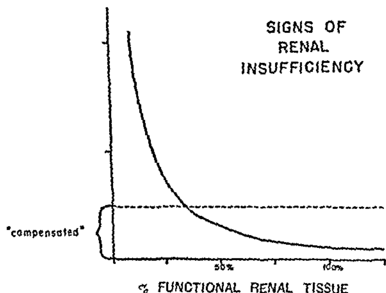


Figure 3 Relationship between functioning renal tissue and signs of renal failure (EPSTEIN F H Reversible uremic states J A M A 161 494–499 1956)

Obstructive Uropathy

Calculi and Crystaluria

A special effort should be made to rule out obstruction as the cause of cessation of urine flow A history of previous attacks of renal colic due to calculi should be sought, and consideration should be given in the history to all causes of calculi, i e, gout metabolic bone disease, hyperparathyroidism, vitamin A deficiency, excessive ingestion of vitamin D and/or soluble calcium salts

The use of triethylene melamine[186] or radiation[195] in the treatment of leukemia, nitrogen mustard in the treatment of Hodgkin's disease,[305] and dibenamide in the treatment of gout[373] have resulted in the rapid mobilization and excretion of uric acid producing ureteral obstruction by uric acid crystals In addition, large amounts of uric acid, other purines and pyrimidines may be deposited in the tubules, further impairing tubular function [127]

CASE REPORT

M O, a sixty four year old white male, was admitted to Mount Sinai Hospital on April 10, 1954, because of the sudden onset of *anuria No urine was obtained by catheterization* The patient had been receiving deep x ray therapy to the axillary and cervical regions for lymphosarcoma Three years previously, a cholecystectomy for cholelithiasis a right nephrectomy for a cystic right kidney, and polypectomy of the sigmoid were performed The diagnosis of lymphosarcoma was established from biopsy specimen Cystoscopic examination and passage of a ureteral catheter into the pelvis of the left kidney disclosed no obstruction Two days before admission to the hospital, the patient complained of a mild diarrhea The patient was ambulatory appeared fairly well nourished, and was not acutely ill or dehydrated The salient findings were a moderate degree of cervical and axillary adenopathy *and a brawny induration of Brunner's shelf*, palpable on rectal examination The prostate gland was not enlarged The cause of the acute anuria was obscure although dehydration resulting from diarrhea was considered He was treated conservatively with fluid restriction intravenous glucose, oral feedings of carbohydrates and fats antibiotics, and intermittent daily gastric lavage A retention catheter was placed in the bladder Oliguria of less than 100

cc. of urine per day persisted, and the blood urea nitrogen rose to 376 mg per 100 ml., creatinine 23 2 mg per 100 ml, uric acid 20 mg per 100 ml, potassium 6 5 mEq per liter, CO_2 combining power 5 9 mEq per liter He was also given enemata of specially prepared potassium free hydrogen cycle, ion exchange resin, and small amounts of 10 per cent glucose and 1/6 M sodium lactate, intravenously Despite six days of oliguria and intense azotemia the patient was well hydrated and rational and demonstrated no uremic symptoms A slight sacral edema was noted on the fifth oliguric day but the lungs were clear The electrocardiogram showed a 3 to 1 heart block with no evidence of hyperpotassemia The diuretic phase began after six days of anuria, April 16, when the patient voided 500 cc. of grossly bloody urine, and reached a peak on April 17 when 5500 cc. of urine were passed Approximately half of this volume was replaced by glucose and electrolyte solutions About 5000 cc were voided in the following twenty four hour period, and the azotemia rapidly cleared, i e, blood urea nitrogen, 44 3 mg per 100 ml, creatinine, 1 6 mg per 100 ml, uric acid 5 1 mg per 100 ml The serum sodium rose to 147 mEq per liter and the CO_2 combining power to 29 3 mEq per liter, indicating the presence of hypernatremic alkalosis His general condition improved, and he was ambulatory although he remained chronically ill and vomited frequently He died suddenly within a few seconds after complaining of substernal oppression on May 3 1954

Autopsy disclosed a generalized metastasis of lymphosarcoma, involving particularly the liver and retroperitoneal lymph glands The right kidney was missing and the left kidney appeared normal except for moderate dilatation of the pelvis The left ureter was imbedded in retroperitoneal tumor mass which compromised the lumen especially at the bladder orifice which was almost completely occluded Histologic examination of the kidney failed to disclose alterations sufficient to account for the acute renal insufficiency The sudden death could not be explained by the autopsy No myocardial infarction was observed and the coronary vessels were patent.

Comment A number of factors combined to produce acute renal insufficiency in this patient, i e, absence of one kidney, partial ureteral obstruction, electrolyte imbalance, dehydration, and an overwhelming load of nitrogenous byproducts from radiation therapy of lymphosarcoma The patient survived both the oliguric and diuretic phases, and the azotemia subsided The sudden death was probably due to complete heart block and ventricular arrest

Other Causes of Obstruction

The accidental injury or ligation of ureters during surgical procedures (traumatic retroperitoneal hematoma"[46]) may produce obstructive uropathy Inadvertent unilateral ligation of a single ureter can produce total anuria if the opposite kidney is either absent or hypoplastic

Diagnostic Procedures, Indications, and Hazards

When obstructive uropathy is suspected, a scout film of the abdomen should be taken immediately and an indwelling catheter placed in the bladder If the scout film gives no clues and urine is not obtained within twelve hours from the indwelling catheter, cystoscopy is indicated in the search for possible obstruction of the ureters by radiolucent calculi or other pathologic conditions If ureteral obstruction is likely, the ureters should be probed singly and the catheter removed from one ureter before exploring the other This precaution is necessary to prevent reflex anuria or possible damage from retrograde dye injected in the presence of preexisting renal damage Some believe that retrograde pyelography is actually contraindicated in acute renal insufficiency Under no *circumstances are ureteral catheters to remain in situ since* they may, reflexly, further inhibit urine formation

RETENTION CATHETERS— PROS" AND CONS"

The common practice of inserting a retention catheter has been justly criticized because the indiscriminate use of this procedure is undoubtedly a factor in the development of ascending upper and lower urinary tract infection [286] We believe that the use of the retention catheter, even for short periods, is a calculated risk which cannot be *circumvented in the oliguric or anuric patient* In critical circumstances, no other method may be feasible for determining urine flow If the patient is having difficulty voiding frequent catheterizations are as harmful as the indwelling catheter When the retention catheter is used, it should be removed and replaced with a sterile substitute every three or four days The catheter should be

irrigated two times daily with 1 to 10,000 potassium permanganate solution [189]

INTRAVENOUS PYELOGRAPHY

Considerable information regarding the nature of obstructive uropathy can be obtained from an intravenous pyelogram, however, in the presence of oliguria or anuria, the renal tubules may suffer from the additional burden of dye excretion thus making intravenous pyelography a questionable and hazardous procedure It is generally believed that an elevation of the blood urea nitrogen above 70 mg per 100 ml is also a contraindication to intravenous pyelography because of poor concentration of dye and consequent failure of the kidneys to visualize Nevertheless, when the cause of urinary suppression remains obscure, intravenous pyelography may still be indicated, for it can disclose atrophic or polycystic kidneys as the underlying cause

Sulfonamide Reactions

Ureteral colic dysuria, flank tenderness, the presence of sulfonamide crystals in the urine, and a history of sulfonamide ingestion readily establish obstructing sulfonamide crystals as the cause of oliguria Cystoscopic examination usually corroborates the presence of the obstructing crystals Gentle irrigation of the ureters with 10 per cent sodium bicarbonate solution should result in immediate and adequate urine flow Sulfonamides can damage the kidney by sensitivity reaction (glomerulitis), intravascular hemolysis, or tubular degeneration, as well as by obstruction [87]

Sulfonamides are no longer as frequently administered to adults because of the hazard of reactions and the increasing popularity of broad spectrum antibiotics Although sulfonamides are still widely, and at times indiscriminately administered in pediatric practice, it appears that the incidence of reactions is low in this age group

The local use of sulfonamides in the form of salves, pastes, powders, nose drops, and chewing gum should be avoided to pre

vent the development of sulfonamide sensitivity and the hazard of subsequent reactions

When the use of sulfonamides is unavoidable, considerable decrease of crystaluria has been reported by the use of combinations of sulfonamides[112] It has been clearly demonstrated that these *sulfonamide combinations are equal to the sum of the individual* components in antibacterial effect[197]

The alkalinization of the urine by concomitant administration of *alkaline salts, such as sodium* bicarbonate and potassium citrate, has also served to reduce the incidence of sulfonamide crystaluria[112]

CASE REPORT

S P, a sixty four year old white male laborer, entered Mount Sinai Hospital on March 14, 1949, because of oliguria of two days duration For five days prior to oliguria, sulfadiazine was given for treatment of a severe febrile bronchitis Five years previously, a suprapubic prostatectomy was performed for the relief of the urinary obstruction of benign [illegible] and had [illegible] nitro- [illegible] g per 100 ml, the creatinine 16 8 mg per 100 ml, and the hematocrit was 43 Sulfonamide crystaluria was noted Oral and intravenous fluids (10 *per cent glucose) were limited to 1000 cc. for 24 hours After a total* of eight days of oliguria (urine flow 150 to 300 cc for 24 hours), the diuretic phase began The hematocrit dropped to 38, and the biochemical and clinical manifestations of azotemia rapidly cleared The patient was discharged in excellent condition on April 1, 1949 He remained in comparatively good health and was gainfully employed until October, 1955, when a right nephrectomy was performed at another hospital because of a persistent, painless hematuria and an intravenous pyelogram that suggested a neoplasm of the kidney No azotemia was detected The opposite kidney visualized normally The removed kidney was almost entirely destroyed by polycystic and pyelonephritic changes He made an uneventful *postoperative recovery*, but [illegible] treatment of a postoperative [illegible] s after the administra [illegible] suppression occurred, [illegible] al (January 26 1956) with preuremic manifestations The blood pressure was 114/70, the

blood urea nitrogen was 174 mg per 100 ml, potassium 5 2 mEq per liter, red blood count 2,450 000, and white blood count 16,400 The oliguria persisted and intense acidosis obtained with a CO_2 combining power of 9 mEq per liter He expired in a uremic state on February 11, 1956, after 17 days of oliguria

Comment This case is an example of a sulfonamide reaction superimposed upon latent kidney damage of a polycystic and pyelonephritic nature The patient remained well for seven years until the overwhelming stress of nephrectomy, postoperative vomiting, and a sulfonamide reaction were superimposed on the previously impaired remaining kidney

Iatrogenic Urinary Retention

The sudden mobilization of anasarcous fluid by mercurial diuresis may produce rapid distention of the bladder and acute urinary retention, particularly in the presence of prostatic hypertrophy

Ephedrine and related drugs[130] increase the tone of the trigone and vesicle sphincter and, consequently, are prone to produce acute urinary retention in males afflicted with prostatism By similar mechanisms, banthine and atropine like' drugs occasionally induce urinary retention Waller[303] reported ten instances of acute urinary retention which he attributed to banthine therapy for peptic ulcer in patients with varying degrees of prostatic hypertrophy

Autonomic blocking agents, such as, hexamethonium,[137] apresoline,[179] ansolysen,[137] and echolyl, in addition to causing bladder dysfunction, can induce acute renal insufficiency in individuals whose renal function is already impaired by depression of the hydrostatic filtration pressure within the glomeruli resulting from the sudden lowering of blood pressure

Acute and Chronic Pyelonephritis

Patients suffering with acute pyelonephritis occasionally develop oliguria and renal insufficiency from obstruction of the ureters by pus The symptoms of chills, high fever, flank pain, frequency, and

dysuria are so characteristic that differentiation from acute renal *insufficiency is not difficult*

Weiss and Parker,[399] in a classical monograph, were among the first to emphasize that patients suffering from recurrent pyelonephritis may terminate years later with malignant hypertension or uremia The disease may have a long latent period during which the process is quiescent and the urine clear These patients frequently give a history of acute pyelonephritis during childhood and flare ups" during pregnancies The symptoms, however, may be forgotten by the patient and, consequently, not elicited in the history Thus, the presenting symptomatology of chronic pyelonephritis may be only that of malignant hypertension and uremia In this final stage, the urine may be remarkably free from evidence of those previous infections which have ravaged the kidneys [79, 80]

Malignant Phase of Hypertension (Malignant Hypertension)

During the terminal stages of the malignant phase of hypertension from any cause, oliguria or almost total anuria not infrequently supervene The history and symptomatology of hypertensive encephalopathy, i e, vomiting, headache, stupor, and particularly neuroretinopathy, papilledema, and a diastolic pressure above 120, differentiate malignant hypertension from acute renal insufficiency *Extreme elevations in diastolic pressure are rarely* observed in acute renal insufficiency Papilledema and neuroretinopathy are the cardinal signs of malignant hypertension Goldring and Chasis,[128] to the contrary observed the absence of neuroretinopathy in 23 per cent of 68 patients suffering from malignant hypertension *In doubtful cases severe anemia is of diagnostic significance in that it usually denotes the presence of chronic renal insufficiency, whereas in malignant hypertension without a substantial degree of azotemia, the red blood count and hemoglobin are usually normal and may even indicate hemoconcentration*

The symptomatology of the malignant phase of hypertension parallels the abrupt, rapid increase in intracranial pressure and cerebral edema so that despite the absence of renal insufficiency the

uremic state is simulated i e tremors convulsions stupor coma

The term hypertensive encephalopathy was introduced by Oppenheimer and Fishberg [78] and is described in detail in the excellent text of Fishberg [108] Volhard[389] applied the designation pseudo-uremia to the symptomatology of hypertensive encephalopathy

The pathogenesis and vascular dynamics of cerebral edema and hypertensive encephalopathy are not yet satisfactorily explained Cerebral vasoconstriction (angiospasm) as suggested by Pal [280] is open to question Transudation of fluid through the cerebral capillaries from increased arterial hydrostatic pressure may be a more tenable explanation Fishberg[108] and Pickering[293] have pointed to the relation between high diastolic pressures and the symptoms of hypertensive encephalopathy and they have emphasized the absence of correlation between these symptoms and the degree of renal impairment

Acute Glomerulonephritis

Oliguria and occasionally total anuria are symptoms of acute glomerulonephritis and if present may simulate acute renal insufficiency Indeed anuria may be the presenting symptom as in a case cited by Fishberg[108] wherein anuria was the only symptom until uremia became fatally evident

In accordance with our definition of acute renal insufficiency acute glomerulonephritis cannot be included within this category However acute glomerulonephritis certainly must be considered as an important *cause* of acute reversible renal insufficiency [48] Despite the current hasty administration of antibiotics acute glomerulonephritis is still a relatively common disease of children It is caused by or follows systemic infections of the type 12 group A beta hemolytic streptococcus It is a curious clinical paradox that the type of glomerulonephritis which follows or is associated with streptococcus infections has a high morbidity but a low mortality rate while the glomerulonephritis with an insidious onset as characterized by the gradual development of a

nephrotic picture, albuminuria, and a pathologic urinary sediment offers a grave prognosis in subsequent years

Acute and subacute glomerulonephritis can be differentiated from acute renal insufficiency from other causes by a history in the former of a preceding acute upper respiratory tract infection or scarlet fever, peripheral or periorbital edema evidence of vascular disease in the fundus, persistent hypertension, a bloody acid urine the sediment of which presents a typical microscopic appearance and the early occurrence of symptoms of cerebral edema and hypertensive encephalopathy

In the early stages of acute glomerulonephritis, symptoms of acute left heart failure may result from the myocardial damage and the sudden onset of hypertension Tachycardia, tick tock rhythm, pulmonary edema, pneumonitis, and cerebral symptoms *simulating encephalitis may be present early in acute glomerulonephritis* Epistaxis, ecchymoses, purpura, and showers of petechiae are also prominent symptoms not often encountered in the early stages of acute renal insufficiency

We observed a patient with renal shutdown wherein a preceding severe upper respiratory tract infection had been treated with sulfonamides In this case, the puzzling question arose as to whether the oliguria or anuria was the result of acute glomerulonephritis or the effect of sulfonamide sensitivity reaction Renal biopsy established the correct diagnosis of acute glomerulonephritis

The clinical manifestations and treatment of acute renal in*sufficiency due to acute glomerulonephritis* are the same as those of acute renal insufficiency from other causes[48] (see Chapter 7)

Renal Vascular Occlusions

Intravascular occlusion of the renal veins or arteries from thrombosis or embolism, and dissecting aneurysm of the abdominal aorta are extremely rare, but may occasionally present the problem of differentiation from acute reversible renal insufficiency Other than the characteristic sequence of symptoms and rapid deterioration observed in the patient with dissecting abdominal aneurysm

no special clues can be gleaned from the literature which are of value in the diagnosis of renal vascular catastrophes

Harrison and his associates[147] studied eleven patients with either radiologic or necropsy evidence of renal vein thrombosis In six of these, dehydration with uremia and oliguria was superimposed on preexistent primary renal disease Since all eleven patients expired, and recovery from this condition has not been reported, renal vein thrombosis must be classified as one of the causes of irreversible acute renal insufficiency

Acute Hemorrhagic Necrosis of the Renal Papillae

Acute hemorrhagic necrosis of the renal papillae is another rare, fulminant usually fatal kidney disease which may simulate acute reversible renal insufficiency In the absence of diabetes mellitus it occurs most often during early infancy and old age The common etiologic factors in many cases appear to be infection and urinary tract obstruction In infancy, congenital valves of the ureters or aberrant arteries produce the obstruction In the older age group obstruction is usually due to hypertrophy of the prostate in the male and to malignancy or calculi in the female The susceptibility of adults to this condition is considerably increased when pyelonephritis or diabetes mellitus is present, particularly the latter Indeed, acute hemorrhagic necrosis of the renal papillae is generally considered an important renal complication of diabetes and was found in approximately 4 1 per cent of autopsies on diabetic patients[408] and in 27 per cent of diabetic patients afflicted with pyelonephritis[222]

Papillary necrosis and hemorrhages have been reported[257] in sickle cell anemia as some of the causes of hematuria in this condition Acute renal insufficiency was reported in a patient with sickle cell trait who died in a hemolytic crisis[373] The azotemia was attributed to glomerular occlusion by sickle cell agglutination

The pathogenesis of ischemic papillary necrosis remains obscure Identical lesions have been produced experimentally in the rabbit by bilateral ureteral ligation following intravenous injection of

bacteria, and by injection of vinylamine Muirhead[202] has produced similar lesions in dogs by ureteral ligation alone

The symptomatology early in the course of the disease is similar to that of acute, fulminant pyelonephritis, i e, chills, fever, flank pain, dysuria, and pyuria Patients afflicted with necrosis of the renal papillae, however, do not respond to the usual therapeutic measures, and within a few days azotemia and symptoms of acute renal insufficiency supervene

Oliguria and anuria were not striking in the experience of Whitehouse and Root [408] Two of their eleven patients, however, had a daily urinary output persistently below 500 cc for twenty four hours A third patient was oliguric on the day of death The urinary alterations although not specific for the disease, include proteinuria, pyuria, and hematuria, in addition to oliguria The presence of a substantial degree of hematuria favors a diagnosis of this condition

A characteristic roentgenographic appearance of the intravenous pyelogram has been described as sling," 'ring" shadows, blunting of the papillary tip [222] According to Whitehouse and Root,[408] the visualization of ragged calices by retrograde pyelography is the only way to establish the diagnosis unless a papillary cast is observed in the urine

Therapeutic procedures which have been attempted include nephrectomy, nephrostomy, and transplantation of the ureters to the colon These heroic procedures usually fail and have not gained acceptance Since the condition once established is so often fatal, effort should be directed to prophylaxis by early detection and elimination of urinary tract obstruction and infection, particularly in the diabetic patient

Although the course is one of rapid deterioration, an occasional patient may recover From the autopsy studies of Robbins and Angrist,[307] it appears that healed, absorbed papillae augment dilatation of the corresponding region of the pelvis of the kidney and thus may be a mechanism of obstructive hydronephrosis

Hepato-Renal Syndrome

The term, hepato-renal syndrome,[54] was coined to describe the symptom complex of acute renal insufficiency associated with advanced liver disease. The syndrome has been the subject of controversy and contention. Most clinicians are reluctant to accept such a diagnosis whereas a minority feel that it is a distinct clinical entity. Some authors have adopted two designations: cholemic nephrosis and hepato-renal syndrome. This nosologic confusion results from the fact that many substances are both nephrotoxic and hepatotoxic. Moreover, patients afflicted with advanced liver disease often suffer from dehydration, electrolyte disturbances, hypoglycemia, bacterial toxemia and other complications which can produce acute renal insufficiency.

We are of the opinion that the term should be dropped, and a more precise diagnosis as to the cause of acute renal insufficiency should be sought.

CASE REPORT

The patient, a fifty year old white male, was brought to the West Side Veterans Administration Hospital because of a sudden onset of convulsions. On admission, however, he was lucid. He had been an alcoholic addict for fifteen years and had been drinking heavily prior to admission. After admission he again had a series of convulsions, he began to hallucinate and ultimately lapsed into coma and expired, 36 hours after admission. He was anuric during this entire period. The duration of anuria prior to admission is not known. He was at all times normotensive and afebrile. The important feature of the physical examination was hepatomegaly extending 6 cm below the right costal margin. The laboratory data disclosed a white blood count of 11,250, hemoglobin 12.4 grams, hematocrit 40, non protein nitrogen 212 mg per 100 ml., total serum bilirubin 1.3 mg per 100 ml., and inorganic phosphorus 11.8 mg per 100 ml. During the known thirty six hour period of anuria, he received 2000 cc of glucose, intravenously, and 500 cc of water, orally.

Autopsy disclosed typical bilateral cortical necrosis of the kidneys, fatty cirrhosis, and old healed subarachnoid hemorrhage, a miliary congenital aneurysm of the right anterior communicating artery, and congenital cysts of the left kidney.

Comment Prior to autopsy, this case was erroneously classified as hepato renal syndrome The cause of this renal lesion is not clear although alcoholism or some undetermined nephrotoxin may be implicated This case also illustrates that complete anuria is usually not due to a reversible renal condition

5

Clinical Aspects of Acute Renal Insufficiency

Symptomatology

The detailed symptomatology of the oliguric and diuretic phases of acute renal insufficiency will be discussed separately although there is a considerable overlap of symptoms in these two stages

A well-defined clinical picture is not apparent during the early stages of acute renal insufficiency since the primary signs and symptoms of renal disturbance are often obscured and overshadowed by the precipitating causes Patients are frequently overhydrated and suffer from symptoms of water intoxication, such as, lethargy, nausea, and headache If the clinician s attention is not directed to the decreased urinary output, or to the azotemia which may occur despite an adequate urine flow, renal insufficiency may not be detected until the appearance of uremic symptoms, i e , nausea, vomiting hiccough, diarrhea, pruritus, muscle twitching, lethargy, hallucinations, and stupor

The clinical picture of acute renal insufficiency varies considerably with the etiology, pathogenesis, rate of onset, duration and severity of the precipitating cause, and the ability of the kidney to withstand the insult If the insult to the kidney is sudden and severe, as in crush injury or massive hemorrhage, the characteristic uremic state may appear quickly A paradoxical situation may obtain wherein the patient recovers from the primary catastrophe only to be threatened by the development of acute renal insufficiency If the causation is slow in onset, as in gradual salt depletion and dehydration, the development of the symptoms of renal insufficiency is insidious and easily overlooked

the changing modes of therapy. The reported variations in blood pressure are probably due to quantitative and qualitative differences in fluid and electrolyte administration Lueckē[213] reported an elevation in blood pressure in nearly all of his cases, and concluded that a moderate rise in blood pressure is one of the cardinal signs of the ' lower nephron syndrome " Grollman[188] declared that blood pressure usually rises during the oliguric phase, often to hypertensive levels and may not decline to normal for several weeks or months ' Waugh[396] observed systolic blood pressures in the 200 to 300 range Howard *et al* [161] reported blood pressure readings of 140/90 in 85 per cent of 42 battle casualties The average maximum blood pressure on the sixth post wound day was 160/90 The military surgeons attributed this mild hypertension to the liberal use of blood and plasma expanders

In our experience, only occasional elevations of systolic or diastolic pressures were observed, and it is our belief that hypertension is uncommon in the conservatively treated patient

CARDIAC MANIFESTATIONS

All too often, early cardiovascular manifestations are overlooked while the clinician s attention is focused on renal symptoms which may be limited to lethargy and nausea during the first week An awareness of the fact that in the early stages of acute renal insufficiency, patients often die from acute pulmonary edema or the cardiac effects of potassium intoxication rather than from uremia is regarded as the most important step of the past ten years in the treatment of this condition [370] One must be alert to the earliest evidences of cardiac weakness, such as, dyspnea, cyanosis, tachycardia, gallop rhythm, pulsus alternans, rales at the lung bases, accentuation of P 2, and cardiac dilatation manifested by an apical, blowing systolic murmur All of these symptoms and signs indicate a state of overhydration and/or potassium intoxication It should be noted that even when intravenous fluids (transfusions, electrolytes, glucose) are withheld, hypertension and cardiac weakness often appear during the oliguric phase It is tempting, therefore,

to suggest that some undetermined cardiotoxic factors are operative under these circumstances Experimental study of these factors is indicated

Potassium Intoxication It is the concensus of most workers in this field that the early recognition and management of potassium intoxication are by far the most troublesome problem encountered in the management of acute renal insufficiency Since a number of diverse methods for treatment of this complication have been developed, and new approaches are under investigation, the physician is perplexed both with the problem of an early diagnosis of hyperpotassemia and selection of the most feasible therapeutic tool

In battle casualties, potassium intoxication developed with great rapidity, often within six days of wounding, probably because of massive tissue necrosis, infection, and repeated blood transfusions [101]

ELECTROCARDIOGRAPHIC CHANGES OF HYPERPOTASSEMIA The symptomatic and electrocardiographic manifestations of hyperpotassemia are not closely correlated with the serum potassium level because the ultimate physiologic effect on the cardiac conduction system is the result of the combined action of a number of factors of which potassium is dominant The other factors augmenting or opposing the effect of increased potassium levels are the pH, serum sodium concentration and especially the level of ionized calcium Acidosis, which is commonly present in acute renal insufficiency, enhances hyperkalemia, whereas alkalosis, which can induce intense renal insufficiency, tends to depress the serum potassium level Hypocalcemia which occurs in most types of renal insufficiency, augments the deleterious effects of hyperpotassemia on the cardiac conduction system Because of these conflicting factors, the physician must rely considerably on serial electrocardiographic tracings for determination of the intensity of hyperkalemia, particularly since the biochemical state is dynamic and varies with changes in therapy and fluctuations in renal function Although

the widespread popularity of the flame photometer has measurabl[y] increased the availability of electrolyte determinations, instanta[-]neous bedside electrocardiogram tracings are certainly more prac[-]tical than repeated serum potassium determinations

The characteristic electrocardiographic changes of hyperpotas[-]semia have been thoroughly studied in recent years by numerous investigators[157, 199, 200, 245] The earliest detectable change is the development of tall peaked T waves The T waves, however, n[...] be of normal amplitude yet discernibly "tent shaped" and sy[m-]metrical With progressive increments in the serum potassiu[m] concentration, the T waves increase in height and acquire narrow base The Q T interval is variable in the early stages of T wave alterations and, according to Levine,[199] may be normal shortened, or lengthened Prolongation of the Q T interval may perhaps be more closely related to hypocalcemia With further increments in potassium concentration, the T waves become even higher and more peaked, and the QRS complexes broaden indi[-]cating intraventricular conduction defects The P R interval length[-]ens while the P waves tend to flatten and disappear The Q T interval becomes prolonged, the rate may decrease, and ultimately, a grossly irregular ventricular rhythm appears In the penultimate stage of intoxication, the QRS complexes assume the form of ven[-]tricular flutter which is often the precursor of cardiac arrest in diastole

Because of the variable influence of other ions on the cardiac conduction system, attempts to precisely equate and correlate the electrocardiographic patterns with the serum potassium levels from patient to patient have not been rewarding However, in a single patient, the electrocardiographic tracings taken during recurrent episodes of hyperpotassemia were repetitive and predictable Hoff[-]man[158] stated that T wave changes develop when potassium levels reach 7 5 mEq per liter, and that death can occur at concentra[-]tions of 10 00 mEq per liter Others[199] reported the appearance of characteristic T wave changes at levels of 7 0 mEq per liter and above *It should be clearly understood that the harmful effects of*

hyperpotassemia are entirely due to increments in the extracellular potassium concentration only and therefore, can develop despite a total body deficit of potassium

An additional factor increasing the extracellular potassium level is the acceleration of protein breakdown associated with stress and shock (Chapter 2) For every gram of tissue protein broken down about 2 7 mEq per liter of potassium are released [368]

Vomiting and diarrhea oppose the hyperpotassemic effects of renal insufficiency because the loss of chlorides induces alkalosis which tends to depress the serum potassium level Moreover gastrointestinal secretions are high in potassium content and thus a considerable amount of potassium is removed when gastrointestinal contents are lost

SYMPTOMS Although electrocardiogram alterations usually precede clinical manifestations the early symptoms of hyperpotassemia such as paresthesias numbness about the mouth generalized weakness and a decrease of the deep reflexes occasionally appear without biochemical or electrocardiographic changes However the advanced symptoms and signs (other than cardiac) of hyperpotassemia such as flaccid paralysis areflexia and respiratory difficulties are always associated with electrocardiographic alterations and increases in the serum potassium concentration Pearson and O'Meara[284] stated unequivocally that clinical evidences of hyperkalemia do not exist without significant and characteristic alterations in the electrocardiogram

Magnesium Intoxication Although increased serum magnesium concentration has been known since 1923 [149, 260, 317] meager information is available concerning magnesium balance in acute renal insufficiency [144, 291] Increments of this ion above the normal level are said to produce a progressive decrease of cardiac neuromuscular and central nervous system function Martin and his associates[270] reported considerable elevation of the serum magnesium level in seven patients during the oliguric phase of upper and lower nephron nephrosis During the diuretic phase serum magnesium

levels were depressed *to values below normal in most instances* This decrement was attributed to the anorexia and consequent decrease in food ingested during the preceding oliguric phase

This subject was recently investigated by Wacker and Vallee[391] employing a multiple channel spectrometer Of twelve patients with renal disease, eleven suffered from acute renal insufficiency and one from chronic renal disease Eight of the eleven patients with acute renal insufficiency had acute tubular necrosis It is important to note that the symptomatology of magnesium intoxication simulates the uremic state, i e, muscular weakness, stupor, and coma Moreover, the symptomatology and electrocardiographic changes of hyperkalemia and hypermagnesemia are similar This may explain the previously mentioned frequent absence of correlation between the symptomatology of acute renal insufficiency the degree of hyperpotassemia, and the electrocardiographic changes of hyperkalemia Wacker and Vallee[391] have postulated that hypermagnesemia may be responsible in part for the symptom complex referred to as potassium intoxication They believe that the increase of magnesium concentration in the serum of patients *with uremia undoubtedly contributes to the uremic state*

They reported that the concentration of serum magnesium in patients with acute renal insufficiency is significantly increased in all cases to a degree paralleling that of potassium In several of their patients, however, the magnesium elevation was disproportionate to that of the potassium They believe that as much benefit from dialysis could be attributed to removal of magnesium ions as to the removal of potassium ions

Pericarditis. Pericarditis, as evidenced by a friction rub, may occur in both acute and chronic renal insufficiency,[390] and does not necessarily parallel the intensity of the azotemia While pericarditis indicates a grave prognosis in chronic renal disease, it is compatible with complete recovery in acute renal insufficiency Whereas pericarditis was reported *in only 18 per cent of patients* with acute renal insufficiency, it was observed in one half of patients suffering from chronic uremia[246]

Pulmonary Changes. We have not observed the specific roentgeno-

graphic pattern of the uremic lung described by Alwall[14] The existence of such an entity is questionable and it is probable that the pulmonary findings of uremia are indistinguishable from the usual type of pulmonary edema associated with heart failure or hydremia

Cardiac Failure—High Output Type The cardiac failure of acute renal insufficiency is apparently of the high output type It is characterized by tachycardia high venous pressure rapid circulation time wide pulse pressure and a poor response to digitalis Friedberg[1 6] in a study of four cases of carbon tetra chloride poisoning also concluded that the heart failure associated with this type of acute renal insufficiency is of the high output variety

HEMORRHAGIC TENDENCIES

A hemorrhagic tendency in acute renal insufficiency evidenced by bleeding from the gastrointestinal tract skin and mucous membranes has been observed Gastrointestinal bleeding has been frequently recorded in military casualties with acute renal in sufficiency[161] The cause of this defect is obscure and may be augmented by anticoagulants used during dialysis procedures

Roth *et al*[313] comprehensively studied the hemostatic defect in forty five uremic patients selected at random Twenty-one of the forty five patients had acute renal insufficiency from a variety of causes including nephrotoxins postabortal sepsis pyelonephritis and necrotizing renal papillitis Twenty three of the patients died Hemorrhage was a contributory cause of death in four cases The principal hemostatic defect was thrombocytopenia which was prominent in twelve of twenty-one patients Other significant hemostatic defects were prolonged prothrombin time abnormal prothrombin consumption and prolonged plasma recalcification and bleeding time

Acute Renal Insufficiency without Oliguria

As mentioned previously acute renal insufficiency can be present without discernible oliguria This condition has been observed

TABLE 4

Tabulation of Cases Reported as "Burnett's Syndrome," "Alkalosis with Renal Insufficiency," and "Salt-Losing Nephritis," Compared with Masked Hyperparathyroidism

Author	Race, Sex Age	Ulcer Sympt Years	Barium Meal	Daily Ca Intake		GI Bleed	Ocular Changes	X ray Bone	NPN* BUN	Ca*	Phos *	Alk Phos	Urine Ca Excret	Course	Antemortem Diagnosis	Autopsy Findings
				Milk	Alk											
Burnett et al [illegible]	W/M 44	33	Pos	2 qt	+++	Pos	Pos	Neg	150 NPN	14 6	10	18 BU	Normal	Died	Burnett's synd	Nephrocalcinosis parathyroids not found, gastric ulcer
	W/M 25	2½	Neg	Mod	++	Not rep	Pos	Peri ost thick	85 NPN	12 8	—	6 8 BU	Normal	Died	Burnett's synd	No autopsy
	W/M 44	25	Pos	Large quant	+++	Neg	Pos.	Neg	198 NPN	12 8	6 6	7 2 BU	Normal	Improved	Burnett s synd	
	W/M 38	12	Pos	3 qt	++	Neg	Not rep	Neg	160 NPN	12 7	7 3	—	Not rep	Died	Burnett's synd	No autopsy
	W/M 55	16	Neg	5 qt.	++++	None	Pos.	Peri ost thick	137 NPN	14	5 9	6 BU	Normal	Died	Burnett's synd	No autopsy
	W/M 54	30	Pos.	7 qt	++++	Pos	Pos	Not rep	131 NPN	11 5	4 6	4 4 BU	Not rep	Improved	Burnett's synd	
Sawyer and Soler[illegible]	W/M 53	7	Pos	Not rep	++	Pos	Not rep	Not rep	319 NPN	—	—	—	Not rep	Died	Salt losing nephritis	Parathyroids not examined, nephrocalcinosis
Miller, Freeman and Heath[illegible]	W/M 41	7	Pos	1 qt.	+++	Pos	Pos	Not rep	232 NPN	11 6	3 4	4 8 BU	Not rep	Improved	Burnett s synd	

Wermer et al	W/M 67	13	Pos.	2 3 qt.	++++	Pos.	Pos.	Met. calcinos s	61 BUN	13 1	4	5 BU	Normal	D ed	Burnett s synd	Parathyroid hyperplasia—m d, cal inosis generalized
Carpenter and Pautler	W/M 25	5	Pos.	1 2 gal.	None	Pos.	Pos.	Neg	273 NPN	17 4	6 1	7 5 BU	Normal	D ed	Burnett s synd	Parathyro d adenoma, osteitis fibrosa, nephrocalcinosis
Murphy Settimi, and Kozokoff	W/M 53	5	Not rep.	Not rep	++++	Pos.	Not rep	Not rep	16 2 NPN	—	—	—	Not rep	Improved	Salt losing nephr tis	
Dufault and Tobias	W/M 57	25	Not rep.	1 qt.	++++	Not rep	Not rep	Not rep	51 NPN	12 8	4	2 6 BU	Not rep	Improved	Burnett s synd.	
	W/M 52	26	Pos.	1 qt.	++++	Not rep	Pos	Not rep	60 BUN	16	4 2	3 0 BU	Not rep	Gastr c resect. Improved	Burnett s Synd.	
	W/M 52	35	Pos.	2 qt.	++++	Neg	Pos.	Not rep.	170 BUN	14 5	10 6	4 0 BU	Not rep	D ed urem a	Burnett s synd	Parathyro d hyperplasia, nephrocalcinosis, metastatic cal
	W/M 50	20	Pos.	1 gal.	++++	Not rep.	Pos.	Neg	68 BUN	12 8	6 0	2 0 BU	Not rep.	Surg explor neck Imp	Burnett s synd.	Micro parathy ro ds normal
Gaber and berg	W/M 45	25	Pos.	1 qt.	++++	Pos.	Pos	Pers ost. thick.	295 NPN	13 5	8 2	4 6 BU	(Sulk) Normal	D ed	Burnett s synd.	Parathyro d adenoma, nephrocalcinosis, met calcinosis
n	W/M 56	6	Pos.	1 gal.	++++	Neg	Pos.	Met. calcinosis hip joint	160 BUN (CO₂ Comb power h gh 86%)	13 5	4 3	Normal	Not rep	Slightly Improved	Burnett s synd.	

/100 ml

TABLE 4—*Continued*

Author	Race Sex Age	Ulcer Sympt. Years	Barium Meal	Daily Ca Intake]		GI Bleed	Ocular Changes	X ray Bone	NPN* BUN	Ca*	Phos *	Alk Phos	Urine Ca Excret.	Course	Antemortem D agnosis	Autopsy F ndings
				M lk	Alk											
Kyle[136]	W/M 49	6	Pos.	3 qt.	++++	Neg	Pos	Slight in crease dens ty	385 NPN	12 1	23 3	22 0 BU	Normal	D ed, uremia	Burnett s synd.	Cong horseshoe kidney nephro-calcinos s inter-stitial nephritis, calcium plugs, gen met. calcifi cation duodenal ulcer parathy ro ds not found
	W/M 42	15	Neg	2 qt.	++++	Neg	Neg	Neg	59 NPN	15 0	5 1	5 3 BU	262 mg 24 hr	Parathyro d adenoma removed improved	Parathy adenoma	
Schols and Keating[137]	W/M 43	3+	Pos	2 qt.	++++	Not rep	Neg	Not rep	120 BUN	13 7	2 6	2 7 BU	259 mg 24 hr	Recovered by d e-tary improvement	Burnett s synd.	
	W/M 52	21	Pos	2 qt.	++++	Pos	Neg	Not rep	94 BUN	12 1	2 8	Not rep	Not rep.	Recovered	Burnett s synd.	
	W/M 49	25	Not rep	240 cc.	++++	Not rep	Neg	Not rep	234 BUN	12 9	4 8	3 2 BU	Not rep.	Recovered, renal calculi	Burnett s synd.	
	W/M 39	6	Pos.	1 qt.	++++	Not. rep	Neg	Not rep	116 BUN	11 8	3 2	2 7 BU	Normal	Urinary calculi, im proved, w th per sistent azotemia	Burnett s synd.	
	W/M 49	6	Pos.	Up to 4 qt.	++++	Not rep	Neg	Not rep	102 BUN	15 6	3 8	3 5 BU	Not rep	improved gastrectomy *recovered*	Burnett s synd.	
	W/M 47	15	Pos.	2 qt.	++++	Not *rep*	Not rep.	Not *rep*	100 BUN	11 2	3 4	4 2 BU	Not rep	Gastroenterostomy bilateral renal cal [illegible]	Burnett s synd.	

	W/F 51	20	Not rep.	1 qt.	++++	Not rep.	Neg	Not rep	126 BUN	13 6	6 2	11 5 BU	Not rep.	Gastrectomy improved	Burnett s synd	Needle biopsy focal cal ificat on of tubules
	W/M 36	4	Pos.	3 qt.	++++	Not rep	Pos.	Not rep	83 4 BUN	12 8	3 8	11 BU	Normal	Gastroenterostomy vagotomy improved	Burnett s synd.	
itchell et al	W/F 45	8	Pos.	1 qt.	None	Not rep.	Neg	Bil. neph rocal cin	19 7 BUN	14 6	3 8	2 4 BU	Sulk ++	Parathyroid adenoma removed, cured	Parathy adenoma	
chneider and Roblnette	W/F 64	4 mo	Pos.	Not rep	Not rep.	Not rep	Neg	Neg	72 BUN	12 5	4 3	Not rep	Sulk. intermit pos.	Parathyroid adenoma removed, cured	Parathy adenoma	
lbright and Kerr	W/M 48	2 mo	Pos.	Not rep.	Not rep.	++++	Not rep	Neph rocal-c n calculi	50 NPN	12 8	2 5	4 BU	Sulk.+	At surgery hyper-plasia parathy-roids d ed mass ve hematemes s 19 mo later	Parathy adenoma	No autopsy
napper et al	W/M 62	10	Not rep.	3 qt.	++++	Not rep	Pos.	Neg	120 BUN	9 3	11 0	12 KA	Sulk. neg	D ed, uremia	Gen. cal-cin Burnett s synd. ?	No autopsy
	W/F 65	14	Pos.	Not rep.	++++	Not rep	Pos.	Met. cal f	43 4 BUN	12 05	5 9	12 0 KA	Sulk.+	Not determined	Burnett s synd (?)	
Venger et al	W/M 47	15	Pos.	Undetermined amount		++++	Pos.	Not rep.	80 BUN	15 5	4 3	7 3 BU	Sulk.++	Bilateralvagotomy improved	Burnett s synd.	
	M 40	13	Pos.	Undeterm ned amount		Not rep.	Pos.	Not rep.	36 NPN	13 8	4 2	6 7 BU	Sulk neg.	Not determined	Burnett s synd.	
	W/F 52	4 mo	Pos.	++++	++++	Not rep.	Pos.	Not rep.	103 5 BUN	15 2	4 4	5 2 BU	Sulk ++++	Cease m lk and al kali improved	Burnett s synd	

* mg./100 ml.

TABLE 4—*Concluded*

Author	Race Sex Age	Ulcer Sympt Years	Barium Meal	Daily Ca Intake		GI Bleed.	Ocular Changes	X ray Bone	NPN* BUN	Ca*	Phos *	Alk Phos	Urine Ca Excret.	Course	Antemortem Diagnosis	Autopsy Findings
				Milk	Alk											
Wegner *et al* [illegible]	W/M 62	9	Pos.	Undetermined amount		Not rep	Not rep	Not rep	23 NPN	12 8	3 4	Not rep	Not rep	Cease milk and alkali vagotomy gastroenterostomy improved	Burnett s synd	
	W/M 55	34	Pos	Undetermined amount		Not rep.	Neg	Not rep	33 0 BUN	15 8	3 6	Not rep	Sulk.+-++	Reduce milk and alkali improved	Burnett s synd.	
	M 45	16	Pos.	Undetermined amount milk Alk ++++		Not rep	Pos.	Not rep	50 0 BUN	17 8	4 1	16 8 BU	Sulk +	Cease milk and alkali improved	Burnett s synd	
	M 51	10	Pos	Undetermined amount		Not rep	Not rep	Not rep	83 0 BUN	14 7	4 8	34 BU	Sulk.++	Cease milk and alkali, improved	Burnett s synd.	
	M 64	6	Pos	Undetermined amount		Pos.	Not rep	Not rep	134 NPN	15 4	6 1	17 0 BU	Not rep	Cease milk and alkali, vagotomy *gastroenterostomy* improved	Burnett s synd.	
	W/M 36	14	Pos.	++++	++++	Not *rep.*	Pos	Not *rep.*	80 BUN	13 1	4 6	13 5 BU	Sulk +	Cease milk and alkali, improved	Burnett s synd	
Agna and Goldsmith[4]	N/F 37	20	Pos	1 qt	Undet. amt.	Neg	Not rep	Absent lamina dura	4 5 BUN	18 0	2 4	4 2 BU	292 mg 24 hr	Subtotal gastrectomy parathyroid adenoma removed, cured	Parathy adenoma	
	F 32	20	Neg	Not rep	Undet. amt.	Pos.	Not rep	Absent lamina dura	5 0 NPN	14 6	3 1	2 4 BU	226 mg 24 hr	Subtotal gastric resection cyst cpa-thyroid adenoma removed uretero lithotomy cured	Parathy adenoma	

* mg /100 ml

most commonly in various salt depletion states classified within the category of low salt syndrome by Schroeder[333] and Danowski[7] In a sense the low salt syndrome constitutes a spectrum of conditions ranging from iatrogenic states (sodium depletion from excessive use of mercurial diuretics and salt restriction diet) to metabolic disturbances such as Addison s disease and salt wasting tubular dysfunctions (so-called salt losing nephritis) (table 4) Under these circumstances the cardinal sign of acute renal insufficiency oliguria is absent

We have seen several such patients with acute renal insufficiency due to salt depletion caused by excessive mercurial therapy in whom the urinary output was adequate or even increased

Parrish[281] reported that two of three patients suffering from acute renal insufficiency associated with alcoholism pulmonary infection and dehydration usually had a daily urine output of more than 1000 cc Teschen[377] in a study of war casualties reported eight patients with considerable impairment of renal function in whom oliguria was either transient or entirely absent He emphasized that acute renal insufficiency without oliguria is not uncommon and that under trying circumstances involving large numbers of critical battle injuries many casualties without obvious clinical uremia may pass unnoticed through the regular chain of evacuation We suspect that many patients suffer a mild degree of acute renal insufficiency without oliguria which passes unnoticed to spontaneous recovery *Thus by relying on oliguria alone as a sign of acute renal insufficiency many cases may be overlooked There is no substitute for repeated non protein nitrogen or blood urea nitrogen determinations*

Diuretic Phase

The first sign of recovery from acute renal insufficiency is an increase in urine flow which may gradually progress to polyuria Swan and Merrill[370] reported a specific quantitative pattern of urine volume during the oliguric and diuretic phases which was not previously described They reported this pattern as one of

"profound reduction in urinary flow," the onset occurring a few hours after the initial catastrophe, and sometimes dwindling to less than 50 cc per day The minimum flow was reached by the second or third day, after which *the daily output gradually increased until* 350 to 400 cc per day were voided Thereafter, the daily urine volume increased rapidly until a balance was reached between intake and output of fluids

Stock,[363] in an analysis of 22 cases of acute renal insufficiency related that diuresis occurred gradually, in step like fashion over a span of four to seven days He arbitrarily established the onset of the diuretic phase as the first day the urine volume exceeds 1000 cc

It should be noted, however, that *despite the onset of diuresis, the biochemical and clinical manifestations of acute renal insufficiency often persist or may even be temporarily intensified* The unusually high incidence of deaths during the diuretic phase should caution against undue optimism based entirely upon the increasing urine flow In one large series,[370] approximately 25 per cent of the deaths attributed to renal insufficiency occurred after the onset of the diuresis In a series of 27 battle casualties [161] nine deaths occurred after the onset of diuresis Therefore, a guarded prognosis and careful observation are required during this phase

The most dramatic symptoms of acute renal insufficiency are often observed during the diuretic phase, due perhaps to rapid water and electrolyte loss In military experience, the level of *azotemia was seldom lowered by a urine volume* of less than 1000 cc per twenty four hours [161] *Failure to replace water and electrolytes judiciously during the diuretic phase may contribute as much to fatality as the excessive administration of these solutions during the oliguric phase*

Mechanism of Diuresis

The phenomenon of diuresis has been attributed to the osmotic effects of metabolic products which accumulate during the oliguric phase This osmotic diuresis has been credited to the excretion of electrolytes and nitrogenous substances (urea, cre

atinine, uric acid) Bull[46] substantiated that this salt and water losing phenomenon is an osmotic effect by demonstrating a linear correlation between the quantity of solute excreted and the urine volume It appears that during this phase, the tubules do a complete turnabout in that during the oliguric phase they indiscriminately reabsorb practically all of the filtrate, while in the diuretic phase they reject large quantities of solute which they are unable to properly reabsorb This is obligatory diuresis since abnormally large amounts of water and electrolytes are sacrificed Unless water and electrolytes are replaced, electrolyte depletion and intense desiccation result The extent to which the untoward effects of this osmotic diuresis can be modified by replacement therapy has not yet been established

Weight Loss

A substantial weight loss (up to 30 per cent of body weight) is generally observed during the diuretic phase[370] This weight loss appears to bear no relation either to the nature of the primary disease cause of acute renal insufficiency or to the duration of oliguria Weight loss is probably affected by several factors, such as fluid and electrolyte replacement and rate of tissue breakdown during oliguria

Fever and Convulsions

A low grade fever of days to weeks' duration is common during the diuretic phase Occasionally, this fever is the result of urinary tract infection from repeated catheterizations ('catheter fever'), but it also occurs when other obvious causes of fever have been excluded and pyuria is absent The cause of this febrile reaction during the diuretic phase is not clear Antibiotics should not be administered unless pyuria is observed or some other definite indication for their use is present

An exaggeration of the neurologic signs of uremia progressing to convulsions and coma is not uncommon during the diuretic phase, and is probably due to rapid changes in osmolarity within the cells

Prognosis

Mortality statistics over the past ten to twelve years are inconclusive During the earlier years improper treatment (mainly overhydration) based upon an incomplete knowledge of pathogenesis and pathology was often a cause of death Unfortunately many physicians adhered to the misconception that oliguria was an invariable sign of dehydration which demanded vigorous administration of oral and parenteral fluids Apparently overlooked was the physiologic axiom that an undamaged kidney is obliged to form at least 300 to 400 cc of urine despite dehydration At present all investigators agree that the forcing of fluids and electrolytes has been responsible in the past for many fatalities

The prognosis has substantially improved since Luecké s series in 1946 [13] when a 90 per cent mortality rate was reported Statistics based on the use of perfusion techniques (peritoneal dialysis artificial kidney intestinal lavage) compared to the use of conservative measures are inconclusive The more critical cases usually receive the most radical treatment and it is conceivable that many patients treated by perfusion techniques could have survived with conservative management

Another cause of misleading statistics is the difficulty *involved* in separating renal deaths from fatalities resulting from the primary disease

Strauss[387 398] declared that factors probably unrelated *to the* kidney must be implicated in many fatal cases since 50 per cent of the deaths in his series occurred during the first six days and it is *unlikely that uncomplicated renal insufficiency could cause death* in such a short time He reported that most of the fatal cases of hemoglobinuric nephrosis observed by him had pulmonary *edema which may have been the cause of death*

According to Strauss and Raisz [368] the non protein nitrogen increment seems to bear little relation to the mortality Lower values were more often encountered in fatal cases than in patients who had ultimately recovered Merrill[246] states that acute renal insufficiency of more than three weeks duration usually indicates an extremely poor prognosis particularly if total anuria is present

6

Laboratory Studies in Acute Renal Insufficiency

The Oliguric Phase

Urinary Findings

While urinalysis may be of aid in diagnosis, there are no specific abnormalities differentiating acute renal insufficiency from other renal conditions and urinalysis is of no value in prognosis Also urinary alterations vary considerably with the etiologic factors producing acute renal insufficiency

REACTION AND SPECIFIC GRAVITY

The reaction of the urine is usually acid (pH 5 5 to 7) and the specific gravity is low and fixed in the vicinity of 1 010[370] A high specific gravity is of great significance for it often indicates a state of dehydration in the presence of tubular function sufficient to concentrate urine This circumstance warrants vigorous fluid therapy According to Howard *et al*[151] uncomplicated dehydration as a cause of oliguria can be excluded by the presence of urinary specific gravity of less than 1 020

SEDIMENT

The urine is often frankly bloody during the first few days but subsequently clears In acute cortical necrosis due to concealed obstetric hemorrhage,[342] the first urine passed is often intensely bloody and may at times consist almost of pure blood Microscopic examination of the sediment frequently discloses red blood cells pyuria of varying intensity and casts of all types including the broad renal failure casts of chronic uremia as described by Addis.[3] The prognostic significance of broad casts in acute renal insufficiency is not as grave as the appearance of such casts in the

urine of patients with chronic renal disease[370] When the pH exceeds 6 0, examination of the sediment is unreliable because of the tendency of formed elements to dissolve rapidly in an alkaline urine

The pyuria which often results from repeated catheterizations is usually unresponsive to antimicrobial agents During prolonged periods of oliguria the urine, stagnant within the bladder and tubing undergoes alterations and may not truly represent the urine as it is formed

PROTEINURIA AND GLYCOSURIA

Proteinuria may be intense and prolonged but usually diminishes gradually during the course of the illness Myoglobin from crush injury and hemoglobin from intravascular hemolysis filter into the urine in substantial quantities and give a positive benzidine reaction

Urine formed during the first hours after crush injury is reddened with myoglobin, in oxy and meta forms and in amounts which may exceed three grams per twenty four hours Other normal constituents of muscle cells such as creatinine, phosphate and potassium, also appear in the urine in large quantities

It is strange that notwithstanding severe tubular damage, the reabsorption of glucose from the filtrate is rarely affected and glycosuria is unusual However, Lowe,[211] using sensitive chromatographic methods for detection of glucose, demonstrated a pathologic glycosuria during the oliguric phase which did not extend into the diuretic phase Gross glycosuria has also been reported in mercury poisoning[171]

Blood Chemistry

Acute renal insufficiency is rapidly manifested in profound biochemical alterations with respect to nitrogenous byproducts electrolytes, and aromatic ring substances

PATHOGENESIS OF AZOTEMIA

Nitrogen retention or azotemia becomes apparent with a rapid rise in non protein nitrogen, blood urea nitrogen, uric acid, and creatinine values Non protein nitrogen values above 300 mg per 100 ml and creatinine values over 20 mg per 100 ml have been recorded in acute renal insufficiency [93] According to Sheehan and Moore,[342] in acute renal cortical necrosis the blood urea nitrogen does not reach the high levels which may be seen in acute renal insufficiency from other causes

Urea excretion parallels both the quantity of protein metabolized and the glomerular filtration rate and may be simply stated by the formula $Q + kGFR \times P$, where GFR = glomerular filtration rate, P = plasma level of urea Q = concentration of urea in glomerular filtrate and k is a proportionality constant (fig 4)

Many factors combine to augment the blood urea level For example, urea clearance is abnormally reduced by a decrease in glomerular filtration rate and/or an increase in back diffusion (reabsorption) through damaged tubules Both of these factors are undoubtedly operative

Ratio of Urinary Urea to Serum Urea Perlmutter[286] believes that the ratio of the urinary urea concentration to serum urea concentration may be a valuable test in the diagnosis of acute tubular necrosis At times the tubules can concentrate electrolytes while they cannot concentrate urea Further studies concerning the significance of this ratio are certainly indicated

Increased Protein Catabolism Increased protein catabolism resulting from shock, hemoconcentration [93] peripheral circulatory failure, and infection will deliver excessive quantities of nitrogenous byproducts to "shocked kidneys already handicapped by impaired circulation Three basic mechanisms are involved in this acceleration of protein breakdown 1) anoxia, 2) disruption of osmolarity between the cells and the extracellular fluid, and 3) toxic destruction of protein Since in the experimental animal this

increased protein catabolism is not inhibited by adrenalectomy[98] it is probably not mediated by adrenal steroids alone

Increased protein catabolism is obviously present when extensive muscle destruction occurs Nitrogenous residues are also absorbed in considerable quantity from large necrotic areas

Strauss and Raisz[368] have calculated that the non protein nitrogen should increase by 12 mg per 100 ml daily in the anuric subject who receives 10 grams of glucose per day and whose insensible water loss is replaced

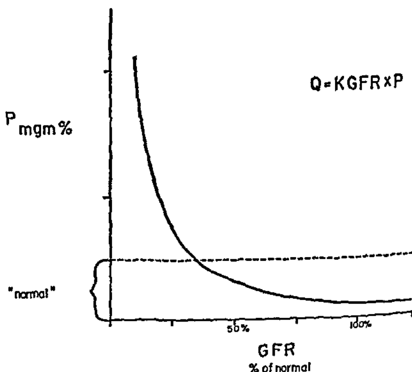


Figure 4 Relationships inherent in excretion of urea Q = quantity of urea formed and excreted k = a proportionality constant GFR = glomerular filtration rate and P = plasma level of urea (EPSTEIN F H Reversible uremic states J A M A 161 494–499 1956)

The mean rate of plasma non protein nitrogen accumulation in a large series of battle casualties was 50 mg per 100 ml for twenty four hours,[161] which is four times the rate calculated by Strauss and Raisz[368] from civilian experience

Remenchik *et al*, [303] in a study of changes in body water compartments by the antipyrine and radiosulfate methods in eight patients with acute renal insufficiency, corroborated the existence of an increased catabolic rate This increased catabolism releases excessive quantities of water and electrolyte which augment the urine volume during the diuretic phase

Increased Nitrogenous Products from Massive Infarction, Hematoma, and Gastrointestinal Hemorrhage The systemic absorption of the nitrogenous products of hemoglobin breakdown from pulmonary infarction hematoma formation and massive gastrointestinal bleeding[32] contributes only slightly to the azotemia which may develop Under these circumstances, the azotemia more probably results from the effects of shock on renal circulation as previously described (Chapter 2) Another mechanism elevating the blood urea level is the physiologic increased reabsorption of urea which occurs when the urine flow is substantially reduced [353] Thus, oliguria, per se, increases the level of blood urea

DISPROPORTION BETWEEN NON PROTEIN NITROGEN AND CREATININE

We have occasionally observed patients in whom the non protein nitrogen and creatinine levels were disproportionately elevated This disproportion was most common in acute renal insufficiency A survey of the English literature revealed a paucity of information on the significance of the ratio of non protein nitrogen or blood urea nitrogen to creatinine especially in conditions other than primary renal disease Bell and Knutson[76] stated that in extrarenal azotemia there is no distinct relation between these two components Fishberg[108] observed that in acute glomerulonephritis and in pre renal azotemia, the increase in urea content of the blood may be considerable before the creatinine value rises Patch and Rabinowitch[292] reported that when the creatinine levels

were normal or nearly normal, symptoms of uremia were usually absent in spite of the high urea values Livermore[106] stated that while a urological obstruction may at first show a normal or low creatinine content with a high non protein nitrogen level, in long standing obstruction, the creatinine and non protein nitrogen values are both proportionately elevated Although numerous studies of the various aspects of acute renal insufficiency have been published, reports on the significance of the non protein nitrogen blood urea nitrogen creatinine ratio are singular Therefore it appeared worthwhile to us to investigate and compare this "ratio" in all azotemia nephropathies, i e, acute renal insufficiency, primary renal disease, and urinary tract obstructions[119]

Of thirteen patients with primary renal disease and non protein nitrogen values above 100 mg per 100 ml, only two had creatinine values below 8 mg per 100 ml, the lowest being 4 4 mg per 100 ml Whereas, of 14 patients with acute renal insufficiency and non protein nitrogen values above 100 mg per 100 ml, ten had creatinine values of 8 mg per 100 ml or less[119]

In our study[119] of this problem on 22 cases of acute renal insufficiency from a variety of causes, we concluded that a creatinine value disproportionately lower than the non protein nitrogen or blood urea nitrogen increment is indicative of acute renal insufficiency

Fishberg[108] offered a plausible explanation for the discrepancy between non protein nitrogen and creatinine values in certain cases of acute renal insufficiency He reasoned that urea is eliminated solely by glomerular filtration while creatinine is eliminated both by glomerular filtration and tubular excretion, therefore, although morphologically the tubules are always involved primarily, the earliest attack is on the glomeruli Fishberg[109] also reported that he observed this same phenomenon of an increase in blood urea nitrogen with normal creatinine, in the first stage of mechanical urinary obstruction Others believe,[248] to the contrary, that this disproportionate rise in blood urea nitrogen is probably an indication of chronic wasting and reduced muscle

mass resulting in decreased creatinine production Ordinarily, however, the rise in creatinine parallels the rise in non protein nitrogen regardless of the cause of renal insufficiency

PHENOL BODIES

The significance of blood phenols and their relation to uremic states has been the subject of considerable investigation and dispute[61, 120, 158, 265] since Bechar[23] first pointed out the similarity between symptoms of phenol poisoning and uremia

Blood phenol levels rise whenever uremic symptoms appear[61, 265] Azotemia without uremia, however, does not produce a rise in phenol levels In our experience, a substantial increase in blood phenol levels does not present as serious a prognosis in acute renal insufficiency as it does in uremia of primary renal origin[120]

ELECTROLYTES

The mechanism of water and electrolyte imbalance in acute renal insufficiency is unresolved, and the serum electrolyte values are unpredictable The levels of serum sodium, chloride, potassium, and bicarbonate should be determined frequently since their direction and magnitude are inconstant and therapy depends upon the alterations observed Often, electrolyte disturbances reflect the preceding therapy rather than changes caused by the disturbance of renal function

In the experience of Strauss and Raisz,[264] serum sodium levels showed no distinct deviation from normal but the chloride and bicarbonate values were lower than those anticipated from the rise in sulfate and phosphate No explanation for this discrepancy was offered

In our experience, the electrolyte pattern commonly consists of a depression of serum sodium, chloride, and bicarbonate levels and an elevation of potassium However, other patterns of elevation and depression of electrolytes have been described Contributing to this inconstancy are factors, such as, therapy, extra

cellular shift of water intracellular migration of sodium lability of skeletal sodium and insensible water loss

Since only small quantities of electrolytes (sodium potassium chlorides sulfates and phosphates) are excreted in the meager urine formed during the oliguric phase the observed hypo electrolemia is probably the result of the migration of these ions (particularly sodium) into the cells

AMYLASE

Altogether plasma amylase has been reported to rise and crises resembling acute pancreatitis have been observed in acute renal insufficiency Meroney *et al* [243] in an experimental study demon strated that the urine plasma amylase is so variable as to be of little diagnostic importance

The Diuretic Phase

Decreased Vulnerability of the Kidneys during the Diuretic Phase

A curious paradox of increased resistance to further insult dur ing the diuretic phase has been pointed out by Welt and Peters [402] This decreased vulnerability has been attributed to the inability of the tubules to concentrate urine Under these circumstances toxic metabolites capable of producing tubular damage cannot be sufficiently concentrated to exert their harmful effects Thus once diuresis has begun additional trauma and stress such as shock or dehydration do not result in a second oliguric phase

Urinary Findings

REACTION AND SPECIFIC GRAVITY

During the diuretic phase except for the absence of glucose the urine is almost identical in composition to glomerular filtrate and has a specific gravity in the range of 1 010 to 1 014 From days to several weeks or more the tubules are unable to concentrate or dilute the urine A blunted response to water loading and a normal to excessive excretion of salt have been reported [370] Therefore a paradoxical situation obtains wherein extreme polyuria exists

without the low urine specific gravity usually observed in polyuric states, such as diabetes insipidus

SEDIMENT

Pyuria persists for several weeks before gradually dissipating This may be attributed to previous catheterizations All types of casts are prominent for some time but ultimately disappear Red blood cells are rarely found after the first week

ALBUMIN AND SUGAR

The duration of the albuminuria varies from several days to months, but glycosuria has not been reported during the diuretic phase

ELECTROLYTES

The large quantities of electrolytes (sodium, potassium, chlorides, sulfates and phosphates) excreted in the urine during the diuretic phase are due to several factors 1) accumulation of these electrolytes during the oliguric period 2) excessive administration of electrolytes 3) inability of the tubules to selectively reabsorb and conserve electrolytes The nature of the renal injury and treatment received during the course of illness determine which of these three factors is dominant

Blood Chemistry

AZOTEMIA

It is important to be aware of the fact that there is often a lag in the fall of blood urea nitrogen with the onset of diuresis and, on occasion, there may even be a transient rise (fig 5)

Occasionally, several days of diuresis will elapse before urea clearance is sufficiently improved to cause a decrease in blood non protein nitrogen level Usually however, the non protein nitrogen, blood urea nitrogen creatinine, and uric acid drop precipitously to normal levels within a few days after the onset of diuresis

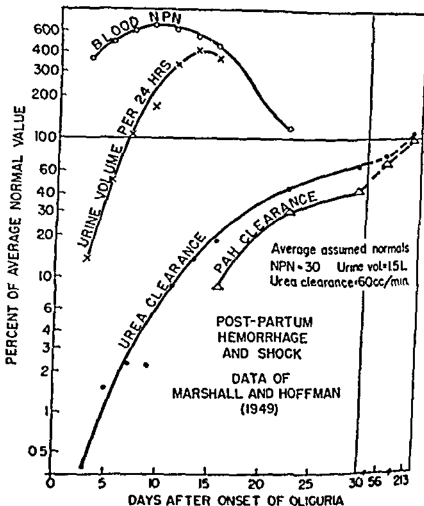


Figure 5 Treatment of acute renal insufficiency Data obtained from patient during diuretic phase after oliguria occasioned by hemorrhage and shock. There is progressive improvement of urea clearance Not until six days following the onset of diuresis however was clearance adequate to cause a drop in blood non protein nitrogen This rise in non protein nitrogen with increasing urea clearance is characteristic of the early phase of diuresis and unless this relationship is realized may give a false impression as to the progress of the renal lesion (MARSHALL D AND HOFFMAN W S Nature of altered renal function in lower nephron nephrosis J Lab & Clin Med 34 31 1949)

ELECTROLYTES

A tremendous loss of water and electrolytes particularly sodium, results in a transient phase of negative sodium balance which occasionally produces hyponatremic manifestations Paradoxically, despite the magnitude of electrolyte loss, the previously depressed serum electrolyte levels now approach the normal range Moreover, hypernatremia and hyperchloremia have been observed during this stage

Recovery Phase

When acute renal insufficiency is the result of shock, the inability to concentrate urine may persist for weeks or months, whereas in kidneys damaged by nephrotoxins, recovery of concentrating powers is more rapid In some patients however, the concentrating and pH regulating functions are not re-established for many months, and occasionally the impairment is permanent

A follow up study of 16 patients who recovered from acute renal insufficiency revealed that although the phenolsulfonphthalein excretion and specific gravity returned to normal within six months the clearance values for inulin and para aminohypuric acid remained impaired in most patients This study showed no correlation between the degree of residual functional impairment and the severity or duration of the acute renal insufficiency [107]

Another follow up study of 14 patients who recovered from acute renal insufficiency demonstrated that although clinical recovery was complete, clearance values remained below normal for up to three years [210]

7

Conservative Management of Acute Renal Insufficiency

Physiologic Principles of Treatment

To properly treat acute renal insufficiency, an understanding of the fundamentals of renal physiology is essential, particularly since there are few other medical conditions in which therapy can so critically affect the ultimate outcome In general the kidney performs two vital functions 1) It eliminates waste products, especially the residues of protein metabolism, maintaining certain of these products (urea, creatinine, and uric acid) at or below a certain level 2) It is the dominant organ regulating the "internal milieu" (water, pH, and electrolyte balance)

In addition, the kidney is involved in certain poorly understood metabolic functions, such as, detoxification and excretion of aromatic ring compounds,[339] and some ill defined facets of carbohydrate and fat metabolism It should be mentioned here that the basic mechanism of the uremic state has never been satisfactorily explained Although phenols[120] and related substances have been strongly implicated as the offending agents, other as yet undetermined factors may be more important

For a short period at the end and immediately following World War II, many patients with acute renal insufficiency were given substantial quantities of water and electrolytes notwithstanding the obvious fact that the oliguric patient is a "closed system" Unfortunately, several misleading theories were advanced in support of this treatment and undoubtedly were responsible for the exceedingly high mortality rate recorded during this period The liberal use of water and electrolytes was based upon these theories 1) Water is the best of diuretics and should be given to break through the "renal blockade" or "open the kidneys" 2) Acidosis

and anemia should be fully corrected to improve renal function 3) Toxic substances producing uremia can be diluted by forced hydration Contributing to the high mortality was a lack of knowledge as to the frequency of acute renal insufficiency and the consequent 'flooding of the patient by intravenous fluids, plasma, and blood in the prophylactic and definitive treatment of shock In the presence of oliguria, attempts to restore a low hematocrit value to normal by means of blood transfusions often resulted in a fatal pulmonary edema

Schreiner and Berman[332] offer two explanations for the ubiquity of overhydration in these patients 1) delayed recognition of oliguria and 2) failure to appreciate the large amount of endogenous water produced by the metabolism of food and body tissue Ten patients transferred from various hospitals to their institution for treatment were overhydrated, some to the point of edema

Accumulated experience has resulted in a better understanding of the dynamics of acute renal insufficiency, and it is generally agreed that conservative management consists of the control of hyperpotassemia and restriction of fluids, electrolytes and protein[44] Differences of opinion are limited to the degree of fluid restriction the type of fluids to be given, and the method or route of administration With general acceptance of the modern physiologic principles of treatment, the mortality and morbidity have measurably decreased

Prophylactic Treatment

The prophylactic treatment of acute renal insufficiency is of prime importance Since hemorrhage and shock appear to be common pathogenetic factors, their immediate treatment is imperative Particular emphasis should be directed toward preventing and reversing hypotension The therapeutic measures, therefore which prevent or reverse shock will reduce the incidence and severity of acute renal insufficiency Thus, the judicious use of blood plasma plasma substitutes, morphine, and oxygen is of utmost importance There should be an immediate but cautious compensation for blood loss together with constant surveillance of urine flow in all

acute surgical, medical, and obstetrical conditions The prevention, or early recognition, and proper therapy of acidosis, alkalosis, and dehydration states materially reduce the incidence of renal insufficiency Meticulous attention to blood typing and cross matching, and careful observation of the patient during transfusion are of utmost importance in reducing the incidence of transfusion reactions

One of the most frequent causes of acute renal insufficiency in the urological practice is hemolysis associated with various transurethral procedures [271] The venous plexus surrounding the capsule of the prostate gland often allows entry of large quantities of irrigating fluid into the vascular system If, as in the past, sterile distilled water is used for irrigation the influx of substantial quantities of water into the circulation can cause intravascular hemolysis sufficient to produce renal shut-down To prevent this catastrophe, various isotonic solutions, such as 1 1 per cent glycine or 4 per cent glucose, have been substituted for distilled water

Frequent determination of the blood urea nitrogen, serum sodium, chloride, potassium, and CO_2 content should be made on all patients intensively treated for congestive heart failure with low sodium diet, mercurial diuretics, and ammonium chloride Ammonium chloride, in the presence of impaired kidney function, is especially prone to produce chloride acidosis when given over a prolonged period (see Chapter 3) Ammonium chloride, therefore, should always be administered intermittently—a few days of therapy, followed by a few days of rest [122]

Vasoconstrictor Drugs in the Treatment of Shock

The widespread use of norepinephrine and related vasoconstrictor drugs for the correction of hypotension and shock should perforce reduce the incidence of acute renal insufficiency The precise effect of these pressor substances on renal blood flow is not clear [170] Norepinephrine is said to diminish renal plasma flow while homeostatic mechanisms within the kidney simultaneously maintain a normal or increased filtration fraction [318]

Mattingly[233] administered L-noradrenaline to two patients for the treatment of hypotensive shock associated with acute renal insufficiency Both patients recovered The shock like state in one *instance was associated with dehydration following hysterectomy* and in the second instance it was associated with intense diabetic ketosis and dehydration He concluded that the increased renal blood flow following restoration of normal blood pressure more than compensates for the intrinsic renal vasoconstrictor action of this substance

Although continuous infusion of L arterenol is of inestimable value in the prevention and treatment of shock in epidemic hemor rhagic fever, this pressor therapy alone is rarely adequate for the treatment of profound shock and does not prevent severe renal insufficiency and other serious complications which occasionally appear with this condition [414]

Boughton and Sommers,[38] *in an autopsy study of eight* patients who died in shock from various causes despite vigorous treatment with Levarterenol (Levophed), suggested that renal spasm of shock is intensified and prolonged by this treatment They observed histologic changes which they attributed to spasm of the renal arterioles and medullary veins

In order to maintain an effective circulating blood volume salt poor concentrated human serum albumin is required in addition to L-arterenol However, the amount of albumin required is consider ably reduced when administered concomitantly with L arterenol

Antibiotics

The treatment of severe infections, such as, fulminant pneu monia, meningitis, and septicemia, with antibiotics has reduced the incidence of peripheral vascular collapse and acute renal insuffi ciency associated with such diseases Antibiotics, therefore, are a vital prophylactic agent Meroney[242] reported a uremia like syn drome in battle casualties *which he attributed to the* toxic effects of bacterial infection and necrotic tissue breakdown (Chapter 3)

Prevention of Intravascular Hemolysis

The use of intravenous alkali in the form of solutions of sodium bicarbonate or sodium lactate has been recommended for the prophylactic and definitive treatment of intravascular hemolysis resulting from faulty blood typing or the accidental intravenous infusion of distilled water [190, 386] During the course of transurethral resection distilled water may also inadvertently enter the vascular system The rationale of alkali therapy is based upon the increased solubility of hemoglobin in an alkaline urine and the theory that the acid hematin already precipitated in the tubules can be dissolved with inhibition of further precipation by the alkalinity of the urine [240] The evidence for this therapy is most tenuous and the hazards involved in the administration of large amounts of alkalies militate against their use in these circumstances We were impressed with the prevention of a severe transfusion reaction by the administration of large doses of cortisone to a patient who inadvertently received 500 cc. of mismatched blood We attributed the favorable result in this disastrous situation to the inhibition of agglutination response by cortisone

Prevention of Potassium Intoxication

A frequently overlooked cause of potassium intoxication is blood transfusions which are often given only because of a desire on the part of the physician for active treatment It must be emphasized that the serum potassium concentration of banked blood increases with the age of the blood [161, 398] The clinical manifestations of potassium intoxication are rarely evident before the fifth day in acute renal insufficiency resulting from traumatic shock [212] Unless the red blood count falls below 3 000 000 or the hematocrit below 25 transfusions are not indicated and may be harmful It has been pointed out that even severe anemia is well tolerated in acute and chronic renal failure [216, 370] Apparently the red cell mass is fixed at lower levels by homeostatic mechanisms for the hematocrit frequently remains between 25 and 30 despite hematinics transfu

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sions, or progression of the azotemia This anemia often extends into and beyond the diuretic phase [246, 370]

The ubiquitous custom of serving fruit juices to all hospital patients as a panacea for ill health undoubtedly contributes to hyperpotassemia in patients suffering from acute renal insufficiency For example, an eight ounce glass of orange juice contains approximately 12 mEq of potassium Other foods high in potassium content which should be avoided are dried fruits, bran flakes, dark rye flour, graham crackers, nuts, cocoa, cane molasses, potatoes beets, raw cabbage, artichokes, raw carrots, beans, peas, parsley, raw spinach, raw parsnips, popcorn, potato chips, and brewer's yeast

Prevention of Iatrogenic Nitrogenous Increments

The administration of antileukemic and uricosuric agents can overtax the kidneys, especially in the presence of preexisting kidney disease [127] An overwhelming nitrogenous load can produce an acute uremic state To prevent this disastrous turn of events all patients given uricosuric or antileukemic agents (6 mercoptopurine, amethopterin, steroids, benemide, x ray therapy) should have blood urea nitrogen and uric acid level determinations prior to therapy If these values are elevated, therapy must be given cautiously with attention directed to signs and symptoms of renal dysfunction During therapy, blood urea nitrogen and uric acid determinations should be obtained, fluid intake should be increased and oral alkalies should be administered to prevent precipitation of uric acid crystals

Management of the Oliguric Phase

Water Balance

Calculation of the exact amount and precise composition of the fluid given to the oliguric patient is one of the knottiest problems encountered in the practice of medicine Accurate measurement of urinary output is, therefore, of utmost importance To direct proper therapy in certain critical patients, the urine flow should be ob-

served at intervals of four to six hours or less rather than relying entirely on a record of the twenty four hour volume

INSENSIBLE WATER LOSS

Numerous intangible factors affect insensible water loss via the lungs and skin Febrile reactions substantially increase water loss by augmenting the metabolism and protein breakdown and increasing the insensible loss through sweating and rapid respirations Elevation of the environmental temperature also increases insensible water loss Each degree of increment above 30 C increases water loss by 13 per cent [246] Variations in respiratory rate also affect insensible water loss but not to the extent which might be anticipated More water is expired during deep, rapid respirations than during slow, shallow respirations Thus, a severely ill patient suffering from acute renal insufficiency with superimposed pneumonitis, high temperature, profuse sweating, and rapid respirations loses considerably more water insensibly than the oliguric patient who is afebrile and breathing normally

RELEASE OF WATER FROM ENDOGENOUS METABOLISM

During the postoperative period, or immediately following severe physical trauma, endogenous metabolism is accelerated, releasing large amounts of water

Elaborate formulas have been evolved for computing the amount of water released by the exogenous and endogenous metabolism of carbohydrates protein, and fat By such computations, it is currently believed that in the average adult 400 cc for twenty four hours is the insensible water loss which should be replaced in addition to the volume lost through sweat, urine, and gastrointestinal contents

WATER REQUIREMENTS

Frequent blood volume determinations by isotope methods have been advocated as an accurate method for regulating fluid administration, but such techniques are not available in most institutions

It is generally believed that the amount of fluid administ orally and intravenously during the oliguric phase should be e to the total quantity lost in the urine, vomitus, and stool, *plus* cc as the estimated insensible loss through the skin and lungs (and Walker,[269] however, take strong exception to this dictum T consider the replacement of 1000 cc as the amount of insens water loss excessive, and regard the administration of fluids by calculation as hazardous They also believe that replacemen vomitus fluid with an equal volume of normal saline is unso and contributes to overhydration These authors emphasize variability of insensible water loss during illness, and the difficul involved in attempts to compute precisely the amount of fluids via the skin, lungs, stools, and vomitus A recent text mistake advises the administration of 2000 cc of fluid during the first of nephrotoxic oliguria [94]

Generally, the insensible water loss in the average, afebrile, n sweating adult in a temperate environment is approximately 1 ml Since about 500 ml is replaced by water of oxidation fr endogenous or exogenous glucose, fat, and protein, the quant of fluid which must be replaced, in addition to the amount lost urine, stool, emesis and Levine suction, should not exceed 500 According to Strauss and Raisz,[368] proper water balance may be tained in a patient, who is receiving only glucose as nutrient, by e pirically supplying 7 to 8 ml of water per kilogram of body weig to cover the usual 'net insensible water deficit

WEIGHT LOSS

It is impossible to maintain the weight and water balance of tl oliguric or anuric patient without the complications of overhydr tion, such as, hypertension and pulmonary edema Therefore is generally accepted that patients may properly lose a small amou of weight, up to 5 kilogram per day Strauss and Raisz[368] belie that a loss of one half to one pound per day is consistent with prop water balance Weight loss of more than one kilogram per day us ally indicates starvation and fluid deficit

A precise record of the daily weight is of inestimable value in computing fluid replacement Although convenient portable scales have been developed for bedridden patients, they are, unfortunately, not available in most hospitals

CALORIC REQUIREMENTS

Since acute renal insufficiency is a self limited condition, provision of adequate calories is not necessary during a one to two week oliguric period Indeed attempts to prevent weight loss by oral or parenteral administration of the total caloric requirements all too often result in hazardous overhydration simply because additional water of oxidation is generated and maintenance of caloric balance demands water as a vehicle The meager calories supplied should consist of carbohydrates or fat in order to reduce exogenous and endogenous protein breakdown the byproducts of which (potassium, nitrogenous residues, sulfates, and phosphates) cannot be excreted by the kidneys

INHIBITION OF ENDOGENOUS PROTEIN CATABOLISM

It is of particular importance to inhibit endogenous protein catabolism because lethal potassium ions are released when body cells are utilized for energy

Carbohydrates Although 100 grams of glucose for twenty four hours are generally considered to have a sufficient protein sparing effect in the ordinary oliguric patient when metabolic activity is accelerated as a result of the severe stress of trauma or fulminant infection, this amount may not sufficiently inhibit protein catabolism and the starvation ketosis of fat combustion Because the administration of large amounts of glucose in limited quantities of water requires hypertonic solutions (up to 50 per cent glucose) which tend to sclerose the veins the use of polyvinyl catheters threaded into the large veins (brachial, cephalic, or even the vena cava) have been recommended [246] Such a catheter can remain in situ for five or six days without harm and permits the gradual ad

The use of intravenous fat emulsions[246] to supply adequate calories has not yet gained wide acceptance because of occasionally associated untoward reactions Subjective reactions of a mild nature such as anorexia, headache, and backache have been reported in a few instances, as well as transient increments in bromsulphaphthalein retention and thymol turbidity Hepatomegaly, splenomegaly, and thrombocytopenia with bleeding have developed in an occasional patient[394] From reports presented recently in a symposium on intravenous fat emulsions, we gather the impression that untoward reactions are infrequent unless the rate of administration is rapid or the patient has advanced liver disease[168, 394] The administration of fat emulsions to two uremic patients with hyperkalemia resulted in a distinct improvement of the serum potassium level[25] Undoubtedly, fat emulsions which can be administered with complete safety will be developed in the near future

Bull[15] advised a basic therapeutic regimen consisting of the intragastric tube feeding of a synthetic diet containing 400 grams of glucose and 100 grams of peanut oil in water to one liter Assuming complete metabolism of the glucose and fat, the total water administered with the mixture is approximately 810 cc In general, the oral administration of fat and glucose emulsions for inhibition of endogenous protein catabolism has met with little popularity because of the resulting nausea and diarrhea and has, in fact, been largely abandoned

The use of fructose[5] instead of glucose solutions has gained substantial recognition based on the theory that fructose has a greater protein sparing action than glucose[246] The intermediary metabolic pathway for the utilization of fructose differs slightly from that of glucose, but the actual advantage of fructose in the management of acute renal insufficiency is not yet established

The parenteral infusion of ethyl alcohol, supplying five to six calories per cc has been suggested as a caloric supplement, but this measure does not appear to have any advantages over glucose Although the parenteral administration of amino acids in the form of protein hydrolysates, such as amigen, may be of definite value

in postoperative wound healing, their use in acute renal insufficiency is contraindicated because of the nitrogenous byproducts

Electrolyte Balance

The regulation of electrolyte balance in acute renal insufficiency is at times utterly perplexing and demands considerable clinical experience and judgement There is a strong tendency for the patient with acute renal insufficiency to develop acidosis and hypoelectrolemia as evidenced by depression of the serum level of sodium, chloride, and bicarbonate ions It is often difficult to determine whether this alteration is a natural homeostatic manifestation a dilution effect, or if it actually constitutes depletion of these ions

SODIUM

When the serum sodium level is decreased, it is important to determine that this decrement is not due to 1) loss of sodium through body fluids, i e, vomiting, fistulae, or diarrhea, 2) iatrogenic factors such as, diuretics or sodium restriction, 3) dilution by excessive hydration with sodium free fluids, or 4) excessive endogenous production of water If none of these factors is clearly apparent from the history, *it must be assumed that the hyponatremia results from adaptive homeostatic mechanisms demanded by the condition*

Although Danowski and his associates[72] attribute the hyponatremia of acute renal insufficiency to water intoxication and dilution, we believe that it is more often the result of disturbances of the mechanisms which regulate the volume (volume receptors) composition (osmo receptors), and distribution of body fluids Elkinton and Danowski[94] have applied the term 'new steady states to the readjustment of these regulators

In our present state of knowledge, it is not known whether this homeostatic" or ' adaption" hyponatremia is the result of shifting of water from the cells into the extracellular compartment in response to decreased osmolarity within the cells, or to a migration of sodium into the cells (particularly bone cells) resulting from alterations in the selective permeability of the cell membrane to sodium and potassium ions

The frequency of this hyponatremia is revealed in the large series reported by Swan and Merrill[370] wherein the serum sodium level was observed to fall below 130 mEq per liter in one-half of the patients, and below 135 mEq per liter in one-third of the remaining patients They believed the incidence of hyponatremia may have been even greater than this if serum sodium determinations had been more frequent They regarded intravenous fluid therapy unquestionably a factor in the development of hyponatremia during oliguria In our experience, however, *hyponatremia was inevitably present during the oliguric phase despite fluid restriction, and therapeutic attempts with corrective solutions served only to accentuate the defect*

We emphasize that hyponatremia as such produces no symptoms or serious clinical consequences Although the literature contains reports on the improvement of hyponatremia by the administration of hypertonic salt solutions,[72, 238] in our experience unless the hyponatremia resulted directly from severe sodium depletion and dehydration attempts to correct this defect resulted only in overhydration, edema, and cardiac failure Danowski[72] also adhered to this concept in an excellent report on the low salt syndrome He stated that of all the hyponatremic states only those due to actual salt depletion or water intoxication are responsive to the administration of hypertonic saline

Oard and Walker[269] also believe that the depression of chloride and CO_2 ions observed in acute renal insufficiency is adaptive, benign and necessary and, therefore, should not be manipulated

In a symposium on renal function, Bull[45] related that he was ' impressed by the fact that very gross changes in chemistry may occur without any symptoms or signs ' He further stated that attempts at improving the ' cosmetic appearance" of the blood chemistry picture are not always wise He cited his experience with a [illegible]

and a chloride level of 50 mEq per liter The administration of two

liters of water in excess of the previous day s urine volume r in symptoms of water intoxication Attempts at correction hydremia by administration of 375 mEq per liter of sodiur ride resulted in further clinical deterioration In short more normal the electrolyte pattern seemed to be, the wo patient became clinically " He concluded that ' as long patient is symptom free, it is better to leave him alone

Thus, in the practical management of acute renal insuffi unless hyponatremia unquestionably results from total bc dium depletion attempts to raise the sodium level by admi tion of sodium bicarbonate solutions, saline or sodium *should be avoided entirely Indeed, Strauss and Riasz*[369] *sta* equivocally that they have encountered no patients with acute insufficiency in whom hyponatremia required any treatment than drastic fluid restriction

However, if it can be ascertained that the hyponatremia questionably a depletion effect, correction of this defect shou attempted with hypertonic sodium chloride solutions in conc tions up to five per cent

Computing the amount of sodium to be administered by s formulas involving estimation of the total body water u yields quantitative values for sodium, the administration of would produce overhydration

POTASSIUM

Unless positive evidence exists that large amounts of pota have been lost with gastrointestinal contents and hypopotasser corroborated by the electrocardiogram and/or a depressed s potassium level, the addition of potassium ions to the therap solutions is contraindicated in the presence of oliguria We this statement despite the fact that potassium depletion can c without clinical or laboratory evidence

Under the circumstances of intense alkalosis, as observed in so-called ' milk alkali or Burnett s syndrome (Chapter 9) r insufficiency can be associated with potassium depletion Howe

even in this situation the administration of potassium is hazardous unless the urine flow is adequate The details of potassium ion in toxication are covered in Chapter 5

CHLORIDE

Of the ions which are depressed in the hypoelectrolemia of acute renal insufficiency, only calcium, potassium and chloride depletion will produce symptoms Muscle cramps, particularly involving the calf muscles, are an outstanding symptom of hypochloremia Ex treme caution, however, must be exercised in the correction of hypochloremia with the oral or parenteral administration of am monium chloride

Ordinarily, the toxic ammonium ion is converted to urea by the liver, leaving an excess of chloride ions However, if administered too rapidly, or given to a patient with liver or renal insufficiency, nausea vomiting stupor convulsions and coma will result[246] We had this experience when treating severe symptomatic hypochloremia with the intravenous administration of 2 per cent ammonium chloride solution in a patient suffering from chronic congestive heart failure and cardiac cirrhosis A few moments after commenc ing the infusion the patient lapsed into coma and regained con sciousness immediately after the infusion was discontinued On the following day, the same response obtained despite a substantially slower rate of infusion

CALCIUM

Symptomatic hypocalcemia frequently develops in both acute and chronic renal insufficiency as a result of the serum phosphate increment and depression of the pH Decreased serum acidity reduces calcium solubility Depression of the ionic calcium level augments the harmful effects of hyperpotassemia on the cardiac con duction system Conversely, calcium ions are the physiologic an tagonist of potassium ions Meroney,[242] consequently, recommended the daily infusion of 100 cc or more of 10 per cent calcium glu conate both as prophylactic and specific treatment of hyperpotas

semia He advised the daily administration of the followi
venous solution

Calcium gluconate, 10 per cent
Sodium bicarbonate, 7 5 per cent
Dextrose, 25 per cent in H_2O (Containing 50 units of regular insulin)
Isotonic sodium chloride solution or 1/6 M *sodium lactate*

Although this amount of calcium is not sufficient to systemic calcinosis or nephrocalcinosis, it may be a hazar patient who is simultaneously receiving digitalis becaus possible harmful effects of digitalis and calcium ions comb

Because the effect of intravenously administered calci conate is transient, Strauss and Raisz[368] advised intramusc ministration (10 to 20 ml of 10 per cent calcium gluconat attempt to prolong its effect However, the advantage of in cular administration is more theoretical than actual and tl ful local reaction negates its usefulness

The correction of acidosis with intravenous sodium bica or sodium lactate solutions will occasionally precipitate h cemic symptoms, such as tetany, by the sudden reduction of hibitory effect of hydrogen ions (acidosis) on neuromuscul tability and a decreased solubility of calcium The routine calcium solutions is not indicated, however, unless potassi toxication or hypocalcemic tetany is evident

Ion Exchange Resins

Cation exchange resins are synthetic polymers with carl side chain groups which substitute hydrogen or ammoniu for other cations, such as, sodium potassium and magnesium effectiveness, orally, for removal of sodium has been well d strated, and the use of resins for this purpose has become a sta therapeutic procedure Ammonium loaded resins have been u eliminate potassium in the prophylactic and definitive trea of potassium intoxication [100, 276, 181] Elkinton and his assoc treated three patients suffering from acute renal insufficienc

ammonium loaded resins The resin was administered orally by Levine tube as a 7 per cent suspension in whole milk and also as a 17 per cent suspension in water Because of vomiting, one patient was given a resin enema of 10 per cent suspension in water Two of these three patients recovered, but because of other concomitant treatment instituted, their recovery cannot be attributed entirely to the use of resins The authors concluded, however, that satis factory removal of potassium as well as depression of the serum po tassium level can be achieved by the use of resins

Knowles and Kaplan[181] similarly reported the treatment of ten patients with acute renal failure from various causes During the oliguric phase, adults received approximately 50 grams of resin orally per day in divided doses with a mixture of glucose and water These authors also concluded that the use of cation exchange resins is an efficient method for reducing or averting hyperkalemia

Burke[48] advised a preparation consisting of 50 grams of carbox ylic acid resin per 500 ml of water with the addition of 4 tablespoons of methyl cellulose to affect a satisfactory suspension This mixture was given in quantities of 250 ml every four hours as an enema to children with hyperpotassemic symptoms due to the oliguria of acute glomerulonephritis After this treatment, improvements in the electrocardiogram signs of hyperpotassemia were noted

Our experience with these substances has been generally unsat isfactory Oral administration is unpleasant and increases nausea The use of resins as enemata has been impractical because of their tendency to form impactions Efforts by Meroney[241] to circumvent this difficulty by the introduction of resins into the rectum within a silk tube were not feasible It must be emphasized that the sub stitution of hydrogen or ammonium ions for potassium, sodium, and calcium ions further increases acidosis Moreover, the hazard of ammonium ion intoxication is ever present (Chapter 3) In addi tion, calcium ions may be eliminated, thereby augmenting hypo calcemia Thus, it appears to us that the use of ion exchange resins for removal of potassium is unsatisfactory and may be abandoned ultimately

Digitalis

Since the heart failure associated with acute renal insuf is of the high output type (Chapter 5), the use of digitalis is (tionable value Elkinton and Danowski[94] pointed out that th of digitalis on the heart, under these circumstances, is inhib hyperpotassemia Consequently, the sudden removal of pot by dialysis or diuresis may produce digitalis intoxication in tient whose digitalization was optimal in the hyperkalemi Moreover, although the potentiation of digitalis by calcium i tionable,[355] the combined use of digitalis and intravenous c may be hazardous

Aluminum Hydroxide Gels

Practically every reference on the treatment of acute re sufficiency advises the oral administration of aluminum hyd gels for precipitating and removing insoluble aluminum phates from the gastrointestinal tract While some evidence that the administration of aluminum hydroxide reduces th dence and frequency of recurrent phosphate calculi[344] we a aware of experimental data establishing the effectiveness o aluminum hydroxide for reducing the serum phosphate le patients with renal insufficiency and consider the administ of this substance of questionable therapeutic value

Antibiotics

A particular effort should be made to focus on local or sys infections which may be obscured by the critical symptoms (patient As emphasized by Meroney[242] infection is an impo factor in the cause of death from acute renal insufficiency Tra shock, and debility make the patient especially vulnerable t fection which in turn, augments protein breakdown and it sequellae Moreover, in the presence of overwhelming infe the protein sparing effect of glucose is negated, electrolyte an ter imbalance is increased, and a general deterioration of th tient ensues

Bull[45] reported that infection was probably the most important factor in 10 out of 17 deaths in a series of 54 patients. Of these 10 patients, 4 had pneumonia, 3 septicemia, 2 peritonitis, and one had pyelitis and pneumonia. All of these infections were resistant to penicillin and streptomycin. In two of the patients infection was probably introduced during the use of the "artificial kidney."

Therefore, the early debridment of wounds, adequate drainage of infected areas, and strict observance of surgical principles are of utmost importance. When clinical evidence of infection appears, such as, leukocytosis, fever, tachycardia, flush, toxicity, or stupor, therapy with a broad spectrum antibiotic is indicated. Whenever possible, the offending organism should be identified by culture and tested for specific antibiotic sensitivity. In the absence of definite evidence of infection the prophylactic use of antibiotics is contraindicated because of the hazard of complicating fungi infections of the gastrointestinal tract which often result from disturbance of the balance of natural bacterial flora. However, when repeated catheterizations are required, or an indwelling catheter is used, the use of antibiotics is indicated to prevent urinary tract infections. The use of masks at the bedside by the house staff and attending physicians has been advocated to avoid cross infection.[246] This strikes us as a rather overly cautious procedure.

Management of Anemia and Hemorrhage

As mentioned in Chapter 5, a rapidly developing normochromic, normocytic anemia is one of the cardinal symptoms of acute renal insufficiency. However, unless the anemia approaches critical levels (hematocrit below 20 to 25), transfusions are not indicated and, indeed, may be hazardous. Attempts should not be made to treat this anemia with hematinics, such as iron, folic acid, vitamin B 12, liver, or cobalt.[246] The anemia of acute renal insufficiency is more probably another adaptive or homeostatic phenomenon demanded by the condition and is well tolerated by the patient.

Bleeding from the gastrointestinal tract, skin, and mucous membranes is recorded in a large number of battle casualties (27 per

cent of 55 patients)[377] The tendency toward purpura a: from the gastrointestinal tract and mucous membrane: be related to the duration rather than the intensity of state The precise mechanism of this bleeding tendency h clarified It is certainly not due to intrinsic defects in : mechanism and remains unaffected by vitamin C or vi It may be secondary to increased capillary fragility resı unknown factors Thrombocytopenia undoubtedly coı the hemorrhagic tendency

Hypertensive Encephalopathy

Hypertensive encephalopathy is infrequently observe renal insufficiency, however, when the cause is acute nephritis, hypertensive encephalopathy is a frequent co and may produce convulsions and death Fifty per cent r sulfate solution, parenterally administered, has long bee ard effective therapeutic agent However, in the prese guria, a state during which hypermagnesemia is a freque cating factor, we regard the use of this drug as hazardous other drugs, such as reserpine and veratrum viride comp equally effective parenterally administered and are co safer

Treatment of Miscellaneous Symptoms and Compli

Nausea and vomiting are among the most troublesome tions, and when present, ingestion of food should be dis Drugs for combating nausea, such as, chloropromazine, dr and bonamine, are available for intramuscular administr should be given a therapeutic trial While chloropromazi zine) appears to be the most effective drug of this group, it duce hepatitis and jaundice and therefore, is contraindica

The diarrhea which has been reported in association w renal insufficiency has not been prominent in our experier we have not observed the reported acute hemorrhagic titis[246]

During the oliguric phase, while the patient is subsı

parenteral glucose, water soluble multiple vitamin supplements should be added to the solutions Ice chips in small quantities may be cautiously allowed to alleviate dryness of the mouth The use of various candies 'sourballs etc, is of questionable value In our experience, these serve only to increase thirst Thirst is a function of intracellular sodium concentration rather than fluid content of the body tissues Marriott[227] states that he has seen men suffering from severe secondary dehydration refuse water Although extreme thirst has been reported in battle casualties with acute renal insufficiency,[161] it is fortunate that the oliguric patient more often rejects rather than demands oral fluids [289] In our experience, an overhydrated or edematous patient will manifest thirst only during rigorous water restriction or following the administration of hypertonic saline solution [16]

Other uremic symptoms, such as, delirium, convulsions, and coma, are quite resistant to specific treatment although parenteral barbiturates, hypertonic magnesium sulfate and calcium gluconate *may be of temporary benefit The administration of magnesium* sulfate, however, is hazardous in the presence of oliguria because of the toxicity of the magnesium ions

Management of the Diuretic Phase

Water and Electrolytes

As previously mentioned, the onset of the diuretic phase may be marked by either a gradual step-like increase in urine output (fig 6) or a sudden increase in volume (as high as 2000 to 3000 cc for twenty four hours) It is of utmost importance to emphasize that the volume of urine formed during the diuretic phase depends in great measure on the state of hydration and electrolyte balance during the preceding oliguric phase Therefore, if the patient was overhydrated and loaded with electrolytes during the oliguric phase, the urine volume during the diuretic phase will be greater than would obtain if water and electrolytes had been more discreetly administered

Although Swan and Merrill[370] attribute profound diuresis mainly

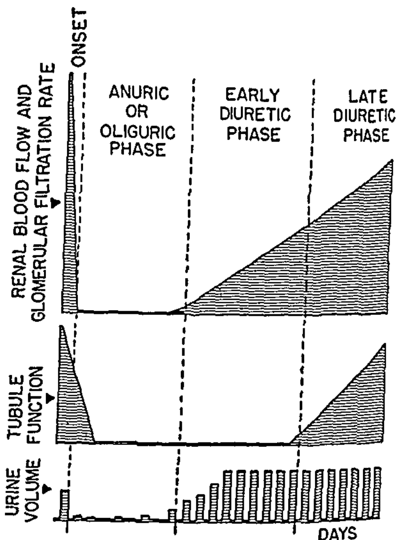


Figure 6 Schematic correlation of the renal function and urinary volu in the three phases of acute renal failure due to tubular necrosis (BULL, G M JOEKES, A M, AND LOWE, K G Renal function studies in acute tubul necrosis Clin Sc, 9 379–404, 1950)

to overhydration, some consider this phenomenon[45] obligatory polyuria with urea as the principal loading solute

An additional important factor augmenting and perpetuating an increased urine volume during the diuretic phase results from the attempt to maintain water balance by replacement, quantitatively and qualitatively, of the entire urinary volume of the patient who was previously overhydrated This common therapeutic error is based on the fallacious axiom, appearing innumerable times in the literature, that urinary water and electrolytes must be completely replaced Adherence to this axiom frequently results in perpetuation of the cycle of overhydration, edema and diuresis On the other hand, an obligatory polyuria occasionally may be observed in a patient who has not been overhydrated In this case, electrolyte depletion and dehydration may result

During the diuretic phase, particularly when sodium solutions are given excessive amounts of potassium may be lost, and oral supplements in the form of potassium chloride tablets are indicated

Thus we emphasize that rigid rules cannot be established for the replacement of water and electrolytes during the diuretic phase[246] The amount and specific character of fluids given during this period must be determined by an evaluation of the state of hydration from bedside impressions and laboratory studies rather than from the quantitative measurement of the urinary loss of water and electrolytes

During the diuretic phase, considerable decrease in the concentrating power of the kidneys as well as a blunting of the response to water loading occurs[370] This imposes a limitation on the amount of solutes which can be excreted Therefore, as in the oliguric phase, caution must be emphasized in the administration of electrolytes particularly sodium It is probably safer at this stage to risk the effects of electrolyte depletion rather than the possibility of hyperelectrolemia which may result from the attempt to replace urinary electrolytes milliequivalent for milliequivalent

The diuresis which marks the return of kidney function represents, to a degree, the excretion of water and salt which accumulated

during the oliguric phase, and does not represent exclusively a loss of salt and water conserving powers of the tubules It is our impression that many cases reported as salt and water wasting syndrome associated with lower nephron nephrosis' are iatrogenic artifacts We hope that by avoiding adherence to inflexible rules and formulas for the regulation of fluid and electrolyte balance the present high mortality (25 per cent) during the diuretic phase will be substantially reduced

Ambulation

Patients should be mobilized as early as possible since prolonged periods of bedrest augment negative nitrogen balance and predispose to hypostatic pneumonia and thrombotic phenomena Even the daily administration of parenteral fluids and the presence of an indwelling catheter should not interfere with the ambulation of the patient The catheter may be clamped for several hours without harm while the patient is ambulatory At the first sign of diuresis the indwelling catheter should be removed, but prophylactic antibiotics should be continued for several more days to avert genitourinary infections

Food Intake

Once the nausea and vomiting have subsided, patients should be encouraged to take food and water as desired The possibility of potassium intoxication vanishes in the presence of an adequate urine flow Elevation of the blood urea nitrogen during the diuretic phase does not preclude the ingestion of protein

As shown by Marshall and Hoffman,[155, 223] there is often a lag of several days from the onset of diuresis to the decrease in non protein nitrogen (fig 5) Moreover, the non protein nitrogen may even rise with the onset of diuresis despite the improved urea clearance and give a misleading impression as to the course of the illness

Anemia

Although the anemia of the oliguric phase may persist for some time after the onset of diuresis, transfusions and hematinics are not

indicated Regeneration of blood usually occurs spontaneously, and the hemogram soon returns to normal

Neurologic Disturbances

Convulsions and other neurologic disturbances reported during the diuretic phase have not been observed by us It may well be that the neurologic symptoms are a manifestation of iatrogenic hyper electrolemia rather than the natural development of the diuretic phase (Chapter 5)

The Therapy of Heavy Metal Nephropathy

British Anti Lewisite, or BAL[20 21 169 207 208] is an effective chelating agent in the treatment of most heavy metal intoxication, i e, arsenic, gold, mercury, cadmium, lead antimony, bismuth, and chromium It is of particular value in the treatment of arsenic, mercury, and gold intoxication The substance was developed during World War II by Stockton and Thompson[364] while working in the laboratory of Professor Peters at Oxford

The therapeutic activity of this material is based upon the strong affinity of its sulfhydryl groups for various heavy metals, thus enabling it to compete with the cellular enzymes to which the metal is bound in exerting its poisonous effects BAL therefore, acts by displacing the heavy metal from its combination with cellular enzyme proteins, forming a non toxic BAL-metal complex, which is then rapidly excreted through the kidneys without producing any demonstrable injury to this organ To date most of the investigations dealing with the therapeutic effects of BAL on heavy metal intoxication have been conducted with experimental animals, and application to human subjects is still preliminary

It is important to emphasize that BAL is ineffective against certain metallic poisons such as thallium and silver, and may actually increase the toxicity of others, such as, lead and selenium

BAL has been dramatically effective in the treatment of bichloride of mercury intoxication and associated acute renal insufficiency The efficacy of the treatment does not depend as much on

the quantity of bichloride ingested as it does upon the time interval between the ingestion and the first intramuscular injection of a sufficiently large dose of BAL Thus, the success of this therapy depends almost entirely upon prompt administration The rapid destruction and excretion of BAL limit the duration of its therapeutic effects to a few hours Therefore, a dose is recommended every four hours around the clock Longcope and Luetscher[207, 208] have reported the largest series of successfully treated cases in an excellent comprehensive review which is our major reference

BAL is available for intramuscular use in a 10 per cent solution in benzyl benzoate and peanut oil Longcope and Luetscher[207, 208] recommend 150 mg for the initial dose in the average adult followed in 4 to 6 hours by another dose of 150 mg If larger amounts of bichloride were ingested a third dose of 150 mg is given 4 hours later Many of his patients received 600 to 700 mg of BAL during the first 12 hours of therapy During the succeeding 24 hours 2 to 3 additional doses of 150 mg are advised Injections are continued for the next few days in diminishing amounts in accordance with the severity of the symptoms

According to the Council on Pharmacy and Chemistry,[20] BAL is available for intramuscular use in an oil base The initial dose is 2 5 mg per kilogram of body weight, followed in one or two hours and again in 2 to 4 hours by 2 5 mg per kilogram of body weight. Up to 12 5 mg per kilogram total dose, may be given within the first twelve hours On the second day, two doses of 2 5 mg per kilogram, and on the third day, one similar dose is recommended The dosage may thereafter be reduced to two injections daily for a total period of ten days or until recovery is complete Larger doses of BAL, up to 5 mg per kilogram, appear to be necessary in more severe poisoning

A number of side effects have been recorded These make their appearance within a few minutes after the injection and disappear within one to one and one half hours The untoward symptoms are recorded as nausea, vomiting headache, burning sensation of the oral mucous membranes and eyes salivation, rhinorrhea, lacrima

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The Radical Treatment of Acute Renal Insufficiency

Prior to the development of various dialysis techniques for the removal of nitrogenous substances potassium ions and other unidentified toxic materials a number of diverse procedures were advocated and indeed carried out in the treatment of acute renal insufficiency Since most of these procedures have been wisely abandoned as futile and at times hazardous they are mentioned here only for historical completeness Among such procedures are decapsulation of the kidney spinal anesthesia sympathetic block blocking of the splanchnic nerves short wave diathermy to the renal area intravenous aminophyllin mercurial diuretics irrigation of the renal pelvis with ureteral catheters and finally exchange transfusion

Exsanguino Transfusions

The heroic procedure of exchange transfusion either with banked blood or continuous cross transfusion with a normal donor has intrigued physicians for two decades[77, 88, 378] Exchange transfusion in the treatment of erythroblastosis fetalis has encouraged investigators to use the procedure for the purpose of removing heme pigments and other nephrotoxic byproducts when acute renal insufficiency results from massive transfusion reaction or other types of intravascular hemolysis The general acceptance and widespread success of this procedure have been reported largely in the European literature

Snapper[357] has advocated this treatment on the tenuous theory that important so-called non dialyzable toxic ions which cannot be removed from the blood by dialysis can be eliminated by complete blood substitution

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The hazards and disadvantages of this procedure are 1) The use of bank blood adds potassium ions which already may be approaching lethal concentration 2) Only a negligible amount of innocuous small molecular dialyzable substances (urea, creatinine, etc) is eliminated by this procedure 3) Complications, such as, serum hepatitis transfusion reaction, or hypervolemia, are inherent in transfusion of large quantities of blood 4) Fatalities have been reported in donors during cross transfusion 5) The infusion of large quantities of blood introduces sodium citrate in toxic amounts resulting in tetany which requires intravenous calcium gluconate for correction Obviously, the shortcomings of this procedure outweigh the hypothetical indications, thus resulting in abandonment of this technique

Dialysis Procedures

Dialysis methods may be divided into intracorporeal and extracorporeal procedures In other words, either by the use of the body surface as a dialyzing membrane, or the temporary removal of the blood from the body for exposure to synthetic dialyzing membranes (fig 7)

Since permeable nitrogenous residues (urea, creatinine, and uric acid) are not the offending agents in the genesis of the uremic state the efficient removal of these substances is not a measure of the effectiveness of a particular dialyzing procedure It is necessary to emphasize that *these nitrogenous residues are innocuous even when highly concentrated Moreover, once the diuretic phase begins their presence in large quantities is beneficial by enhancing solute diuresis* The evaluation of a particular dialysis technique should be based entirely upon its ability to remove potassium to properly regulate the concentration of other ions, and to adjust body water

Intracorporeal Dialysis

GASTROINTESTINAL LAVAGE

The earliest attempts toward removal of nitrogenous byproducts were based upon the fundamental physiologic observation that dur

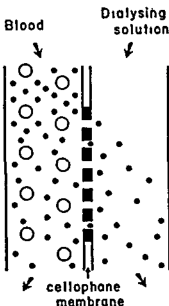


Figure 7 Principle of dialysis across a cellophane membrane The large open circles on left represent red cells and protein molecules which are too [illegible]

transfer and are not shown (ELKINTON J R AND DANOWSKI T S The body fluids basic physiology and practical therapeutics Baltimore The Williams & Wilkins Co 1955)

ing uremia a significant quantity of urea is excreted into the gastrointestinal tract [1] Various portions of the gastrointestinal tract have been utilized as a dialyzing membrane Ordinarily a double lumen tube is placed within the small bowel [2 6] The hypertonic perfusing fluid empties into a proximal opening and is withdrawn through a distal opening several feet beyond thus employing the intervening portion of the bowel as a dialyzing membrane This method of dialysis has been applied largely by continental investigators par

ticularly by Hamburger[14*] in Paris but has gained only a meager acceptance in the United States

Other methods of lavage which have been tried with only minimal success are 1) the introduction of the perfusing fluid through a Levine tube threaded into the small bowel and collection of the fluid by rectal suction thus perfusing the entire gastrointestinal tract [175] 2) lavage of the stomach and 3) lavage of the colon by rectal tube [76]

SALINE CATHARSIS

Another approach is the induction of diarrhea by the oral administration of hypertonic magnesium or sodium sulfate solutions [*46] Without doubt substantial amounts of potassium and water can be removed in this fashion but the procedure cannot be properly controlled and is generally debilitating to the patient

MISCELLANEOUS PROCEDURES

A surgically isolated loop of small bowel has been employed as a dialyzing surface in the treatment of chronic experimental uremia [407] In an attempt to combine the relative merits of intra and extracorporeal dialysis Schloerb[3 4] devised a method in which a closed seven foot cellophane tube is introduced into the intestine by jejunostomy under local anesthesia An appropriate dialyzing fluid is intermittently perfused through the cylinder A preliminary report of the application of this technique on experimental animals is encouraging Obviously these drastic measures are contraindicated in acute renal insufficiency of short duration

SUMMARY OF GASTROINTESTINAL LAVAGE

With the exception of the cautious moderate use of oral sulfate solutions (saline catharsis) it is our belief that all forms of intestinal lavage should be abandoned because the gastrointestinal tract is not an inert semipermeable membrane except perhaps for water and urea Electrolytes such as sodium potassium calcium and phosphates are selectively secreted and absorbed under the control of complex humeral mechanisms independent of the relative

concentration gradients between the intestinal dialysis fluid and the blood [216] Moreover, as shown by Brun,[42] a distinct difference exists between the excretion by the intestinal mucosa of urea and other substances, such as, uric acid, creatinine, and phosphates Thus, while intestinal lavage will remove a certain amount of urea and potassium, water and electrolyte balance is affected only to a minor degree Although intestinal perfusion in experienced hands is a safe, effective method for adjusting fluid and electrolyte balance, in our opinion it is not generally recommended in the routine therapy of acute renal insufficiency

PERITONEAL LAVAGE

The extensive peritoneal surface (approximately 22,000 sq cm) has long been utilized as a living dialyzing membrane for experimental and therapeutic purposes [104 113 297] In contrast to the intestinal mucosa, the peritoneum as an inert membrane has no active excretory or reabsorptive function However, it does permit the free exchange of water, small permeable molecules and ions between the blood and the peritoneal cavity in either direction until equilibrium is reached Thus, permeable nitrogenous residues and electrolytes rapidly diffuse across the peritoneum into appropriate perfusates while protein does not pass the barrier As demonstrated by Darrow,[75] considerable shifting of body water between the extra and intracellular compartments results when the tonicity and ionic concentration of the peritoneal perfusing fluid are varied With the use of an isotonic (5 per cent glucose), electrolyte-free, perfusing solution, sodium, chloride, potassium, and other ions can be removed, and by adjusting the tonicity of the fluid, the total body water can be increased or decreased at will

Prior to the important investigations of Frank, Seligman, and Fine [113] peritoneal irrigation techniques remained primitive because of certain inherent limitations For example, the solutions previously used did not correct acidosis or hypocalcemia, excessive amounts of water were absorbed from the perfusing solution, protein and vitamins were lost and most important of all, peritonitis often developed from external contamination and/or actual mi

gration of colon bacilli into the peritoneal cavity across the intact intestinal wall These investigators modified the perfusing solution and made improvements on other details of the technique so that its limitations have been largely corrected Of eighteen patients treated by this method, only four recovered [113] However, this mortality rate does not negate the effectiveness of the procedure because many of the cases were beyond salvage and utilized as experimental subjects mainly for the purpose of perfecting a hopeful therapeutic method The hazard of infection despite massive antibiotic therapy remains the principal objection to peritoneal lavage

Various techniques for peritoneal lavage have been described and advocated Grollman[138] applied intermittent lavage with a single, small, perforated polyethylene tube introduced into the peritoneal cavity through an ordinary paracentesis trochar He allowed the perfusate to remain within the peritoneal cavity for one and one half hours to establish equilibrium with the blood before siphoning He advised 6 to 12 exchanges of 2 to 3 liters at two hour intervals, and allowed the polyethylene tube to remain within the cavity during the entire procedure

Strauss and Raisz[368] reviewed the American literature and found 52 cases treated with long term peritoneal dialysis There were 29 deaths in this series and a high incidence of pulmonary edema and peritonitis Thus, although the overall results were poor, the effectiveness of the method for removing urea and potassium was clearly demonstrated Strauss and Raisz[368] concluded that, in general, peritoneal dialysis ' has been improved to a point where it must be considered a useful and potentially lifesaving procedure in acute renal failure

Legrain and Merrill[196] described in detail what appears to us a most satisfactory method for short duration (usually less than 15 *hours*), *continuous irrigation* of the peritoneal cavity It is not within the scope of this volume, however, to present a description of this method, and the reader is referred to the original work Furthermore, since we have had no personal experience with dialy

sis methods, we cannot justly evaluate the relative merits of the various peritoneal dialysis techniques

Extracorporeal Dialysis

Abel[1] in 1913 was probably the first to dialyze the blood of living animals, but it was not until 1944 that Kolff[183 185] developed an apparatus called the artificial kidney for dialyzing the blood of human subjects suffering from acute renal insufficiency Thalhimer,[378] who pioneered in the use of heparin for cross transfusions in dogs rendered azotemic by nephrectomy, introduced heparin as an anticoagulant during the use of the artificial kidney' The recent widespread use of the flame photometer for the rapid determination of electrolyte concentration added considerable impetus to the development of more refined methods of dialysis As observed by Snapper[338] however, the term artificial kidney' is a misnomer, for *although the method may remove toxic potassium ions as well as permeable nitrogenous residues (urea, uric acid, and creatinine), it does not substitute for certain vital metabolic functions of the kidney*

Snapper[338] further emphasized that the uremic state is not dependent upon the retention of the small, molecular, permeable, nitrogenous byproducts which should have been filtered by the glomeruli and drained by the tubules The threat to life presented by acute renal insufficiency in addition, of course, to potassium ion retention, may well be inherent in the impairment of vital tubular functions i e, 1) secretion of large toxic molecules, 2) synthesis, and 3) detoxification by beta oxidation Thus certain large, toxic molecules which do not pass through semipermeable membranes must be secreted or detoxified by the tubules and, therefore, can not be removed by the artificial kidney

Since failure of oxidation and detoxification of noxious substances continues during the oliguric phase removal of dialyzable products by the artificial kidney may not be lifesaving In short, *dialysis substitutes only for glomerular filtration and excretion but*

does not replace vital tubular excretory and non excretory detoxifying functions This may account for the rise in blood phenol concentrations which we observed in all our patients with acute renal insufficiency who developed uremic symptoms

PHENOL BODIES

The significance of phenols in the blood and their relationship to uremia like states have been the subject of considerable investigation and dispute since Bechar[23] first pointed out the similarity of phenol poisoning to uremia From our investigations *we conclude that although* an elevated blood phenol concentration offers a poor prognosis in patients afflicted with primary renal disease in acute renal insufficiency a high phenol concentration may be reversible with clinical improvement of the patient[120]

ARTIFICIAL KIDNEY[35, 40, 216, 244, 273]

At present three general types of apparatus 1) Kolff Merrill[183, 184, 185, 246, 370] 2) Alwall[12] and 3) Skeggs Leonards[318, 351] (fig 8) are *being used successfully while undergoing continual modifications* and improvements All three methods are based upon the same general *principle of passing arterial blood under aseptic conditions* through a cellophane container (either tubing or flat sheets) immersed *in a dynamic dialyzing solution* the contents of which can be varied at will In most of these apparatus the cellophane through which the blood must pass is wrapped spirally around a drum which is immersed in the perfusing fluid The apparatus must first be primed with compatible blood After exposure to the synthetic dialyzing membrane the blood is returned to the body by vein In addition the patient must be given substantial quantities of heparin and broad spectrum antibiotics

Merrill s[246] most important refinement in the apparatus originally suggested by Kolff[183, 185] is the addition of a hood over the rotating drum in order to maintain a partial pressure of CO_2 Skeggs and Leonards[351] developed an apparatus in which the blood is separated from the dialyzing perfusate by flat sheets of cellophane

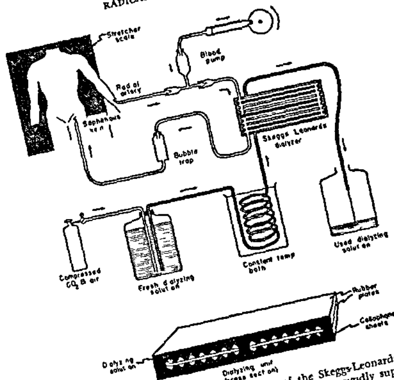


Figure 8 Extracorporeal dialysis circuit of the Skeggs-Leonards artificial dney Blood flows between two sheets of cellophane rigidly supported by ooved plates diffusible solutes exchange with the dialyzing solution passing rough the grooves The sets of plates are connected in parallel and then in eries Blood is pumped from the radial artery by positive-negative pressure through the dialyzer and back through a bubble trap to the saphenous vein Dialyzing solution is forced by CO_2 and air pressure through a constant temperature bath into the dialyzer and out to a discard carboy it is not recirculated Because of the rigid support the apparatus may be used as an ultrafiltrator as well as a dialyzer (Bluemle L. W, Jr., Anderson L. D, and Elkinton J R Use of artificial kidney Tr & Stud Coll Physicians, 20 157, 1953)

Alwall in Sweden[12] and Murray in Canada[264] have independently altered the original apparatus and reported considerable success In the United States, the most widely used apparatus is the or originally designed by Kolff[183, 185] and modified by Merrill[248]

Numerous other types of apparatus have appeared none of which has as yet been given adequate experimental and clinical trial

It is the concensus of the workers in this field that although the Kolff[183, 185] apparatus in its present state is an effective means of dialysis, many defects remain to be corrected, i e, 1) The hazard of infection is ever present 2) The cellophane tubing is fragile dis tensible, and occasionally results in fatal hemorrhage into the machine 3) The mechanical handling of the blood by pumps and coupling may result in hemolysis 4) The use of heparin as anticoagulant often results in excessive bleeding 5) Hypertensio occasionally develops with high rates of blood flow 6) A large bod of trained personnel is required for its operation 7) The apparatu is massive unwieldy, and difficult to transport A review of the specific details of each method is not included in this volume because of the current and continuous modifications and improvements that will be forthcoming from renal centers For details on each type of dialyzer, the original sources may be consulted

INDICATIONS FOR EXTERNAL DIALYSIS

It is not our intention to take sides in the question of conservative treatment versus the more radical methods of therapy, particularly various types of dialysis The management of a particular patient must depend largely upon the equipment and techniques available At present the elaborate apparatus, trained house staff, nurses technicians, and laboratory procedures required by dialysis methods are available in only a few institutions Also in the average hospital of 400 beds or less the occasion for dialysis is so infrequent that maintenance of these elaborate facilities is not feasible Most patients, therefore, must of necessity be treated by conservative techniques unless transferred to 'renal centers

Some believe that the recent reduction in mortality rate of acute

renal insufficiency may well be attributed to the proper management of infection and water and electrolyte balance, rather than to the introduction and refinement of dialysis methods[45]

Indications for the use of external dialysis in the treatment of acute renal insufficiency are by no means clear-cut It is generally believed that the conservative measures previously outlined will certainly suffice in most cases of uncomplicated acute renal insufficiency The notable reduction in mortality rate through modern, skilled, conservative management has lead many physicians to the misconception that dialysis techniques are never indicated We take the position that there should be no argument between conservative measures versus the artificial kidney Although the average, previously normal individual can survive up to three weeks of simple oliguria under conservative treatment, the development of complications (infection, hyperpotassemia and uremia) warrants the use of the artificial kidney Prolonged oliguria and anuria alone are not indications for dialysis

When acute renal insufficiency is due to trauma or fulminating infections deterioration of the clinical state often occurs early, and as soon as practicable, the patient should be transferred to a 'renal center' where vivodialysis is available As stated by Merrill,[246] whose experience with the artificial kidney has been most extensive, the onset of diuresis and advent of complicating factors cannot be predicted by even the most experienced clinician, therefore with each case, an arbitrary time limit should be set, after which dialysis will be available if necessary In this regard, Merrill[246] has further pointed out that small increments in urine volume may not necessarily imply clinical improvement and under no circumstances should the use of the artificial kidney be postponed until all other measures have failed

According to Elkinton and Danowski[94] the overall mortality rate, even with good conservative therapy, is still 50 per cent Therefore, the artificial kidney must be considered as a valuable adjunct to good conservative management, and does not necessarily represent radical treatment They believe that dialysis should be in

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Alwall in Sweden[12] and Murray in Canada[264] have independently altered the original apparatus and reported considerable success In the United States, the most widely used apparatus is the one originally designed by Kolff[183, 185] and modified by Merrill[246]

Numerous other types of apparatus have appeared, none of which has as yet been given adequate experimental and clinical trial

It is the concensus of the workers in this field that although the Kolff[183, 185] apparatus in its present state is an effective means of dialysis, many defects remain to be corrected, i e, 1) The hazard of infection is ever present 2) The cellophane tubing is fragile, dis tensible, and occasionally results in fatal "hemorrhage" into the machine 3) The "mechanical handling" of the blood by pumps and coupling may result in hemolysis 4) The use of heparin as an anticoagulant often results in excessive bleeding 5) Hypertension occasionally develops with high rates of blood flow 6) A large body of trained personnel is required for its operation 7) The apparatus is massive, unwieldy, and difficult to transport A review of the specific details of each method is not included in this volume because of the current and continuous modifications and improvements that will be forthcoming from renal centers For details on each type of dialyzer, the original sources may be consulted

INDICATIONS FOR EXTERNAL DIALYSIS

It is not our intention to take sides in the question of conservative treatment versus the more radical methods of therapy, particularly various types of dialysis The management of a particular *patient* must depend largely upon the equipment and techniques available At present, the elaborate apparatus, trained house staff, nurses tech nicians, and laboratory procedures required by *dialysis methods* are available in only a few institutions Also, in the average hospital of 400 beds or less, the occasion for dialysis in so infrequent that maintenance of these elaborate *facilities is not feasible* Most pa tients, therefore, must of necessity be treated by conservative tech niques unless transferred to "renal centers"

Some believe that the recent reduction in mortality rate of acute

tension persisted until the diseased kidneys were later removed in two stages

This incredible achievement undoubtedly will stimulate and renew attempts to surmount the obstacles of homotransplantation so that man will ultimately have more that his own kidneys for reserve

stituted as early as the fifth or sixth day of oliguria A bleeding tendency, especially gastrointestinal or intracranial, constitutes an absolute contraindication to dialysis

Schreiner and Berman[332] reported that obstetrical patients comprised over 30 per cent of those patients with acute renal insufficiency whose clinical course warranted hemodialysis This included such conditions as abruptio placenta, abortion, eclampsia clostridial infection, and intravascular hemolysis

The documenting at renal centers of hundreds of clinical trials and the beneficial effects of the artificial kidney as evidenced by electrocardiographic and biochemical improvement, amelioration of symptoms, and a sense of well being leave no doubt that under the proper circumstances the artificial kidney has a permanent place in the treatment of acute renal insufficiency

Renal Transplantation

A review of acute renal insufficiency would be incomplete without some mention of homotransplantation of the human kidney In dogs, homotransplants survive only 10 to 14 days despite attempts to combat with steroids the antibody response which ultimately destroys the transplanted kidney[247] A kidney transplant from a dizygotic cattle twin, however, survived and functioned for nine months Most of the attempts at transplantation procedures in human subjects have met with failure, however, in a few cases, a kidney transplanted into the thigh functioned adequately for up to five and one half months

The favorable result of skin homografts between identical human twins led Merrill and his group at the Peter Bent Brigham Hospital[247] to successfully transplant a kidney from one healthy human subject to his identical twin who was suffering from chronic uremia and malignant hypertension This dramatic procedure was attempted only after tissue compatibility was substantiated by the persistent viability of a skin homotransplant Although the uremic symptoms cleared phenomenally, the hyper

Part II

Reversible Chronic Renal Insufficiency

9

Disturbances of Calcium Metabolism Associated with Potentially Reversible Chronic Renal Insufficiency

An important group of potentially reversible chronic renal insufficiency is that associated with disorders of calcium metabolism which often result in nephrocalcinosis i e 1) primary hyperparathyroidism,[83] 2) hyperparathyroidism versus the milk alkali (Burnett s) syndrome,[17, 49, 188] 3) vitamin D and irradiated sterol intoxication,[2, 57, 71, 300] 4) sarcoidosis[125, 180] 5) hyperchloremic acidosis[134] 6) Fanconi syndrome,[102, 191, 236] 7) idiopathic hypercalciuria[36, 105, 204] 8) prolonged skeletal immobilization,[6, 159] 9) excessive administration of androgens and estrogens[153] 10) thyrotoxicosis,[311] 11) leukemia[234]

Primary Hyperparathyroidism

The clinical and biochemical aspects of the usual forms of hyperparathyroidism are well described in the several standard texts[8, 306] and need not be reviewed here However, when the cause of azotemia is obscure, especially in the absence of hypertension, a low CO_2 combining power, and retinopathy, hyperparathyroidism should be suspected To the contrary Hellstrom[150] believed that hypertension probably due to tubular damage occurs in hyperparathyroidism

Primary hyperparathyroidism produces two distinct types of renal disturbance 1) renal calculi and 2) nephrocalcinosis These two complications of hyperparathyroidism are mutually exclusive entities in that, for some unknown reason those patients afflicted with hyperparathyroidism who develop recurrent calculi usually are free from extensive nephrocalcinosis, and those afflicted with nephrocalcinosis rarely develop calculi[8] For the sake of complete

hour urinary excretion of calcium was low and inconsistent with hyperparathyroidism

CASE REPORT

The patient, a forty three year old negro, entered the West Side Veterans Administration Hospital on November 28, 1955, because of recurrent episodes of right flank pain, chills, fever, frequency, and pyuria over the past year A gonorrheal infection in 1936 resulted in a urethral stricture with dysuria and frequency ever since. Physical examination was not remarkable except for a moderate degree of flank tenderness. The blood pressure was 140/100 The non protein nitrogen

b

1

r

and a normal renal pattern on the left The urine cleared, and the patient was about to be discharged when the serum calcium and phosphorus levels were requested because of a questionable calcification of the right kidney Surprisingly, hypercalcemia (calcium 15 mg per 100 ml) and hypophosphatemia (phosphorus 1 8 mg per 100 ml) were discovered Repeated serum calcium determinations on a low calcium

reaction was strongly positive despite a 100 mg calcium diet The twenty four hour excretion of calcium was not determined A large 3 × 2 cm parathyroid adenoma was removed from the right cervical area The patient made an excellent postoperative recovery A positive Chvostek's sign was controlled with oral vitamin D and calcium The non protein nitrogen receded to 28 mg per 100 ml, and the entire biochemical picture returned to normal

Comment This patient was afflicted with two unrelated conditions 1) a urethral stricture with pyelonephrosis, and 2) hyperparathyroidism The first condition masked the second which was only inadvertently discovered because a suspicion of the presence of a renal calculus led to a search for hyperparathyroidism The prompt correction of the hyperparathyroid state reversed the mild azotemia and undoubtedly prevented further renal damage

At the Mayo Clinic, [256] primary hyperparathyroidism is diag

ness it should be noted that patients with hyperparathyroidism m manifest a third type of renal dysfunction[9] caused by the diure effects of hypercalciuria and characterized by anemia a slight e vation of the non protein nitrogen and a polyuria so intense to simulate diabetes insipidus

CASE REPORT

The patient a forty nine year old negro housewife entered Co County Hospital on October 25 1955 complaining of low back pa polyuria polydipsia and nocturia Three years previously bilater renal calculi were observed on roentgenogram but she was not treate The blood pressure was 140/70 and she did not appear acutely il Urinalysis disclosed the specific gravity of 1 004 albuminuria (3 to plus) and a persistently positive Sulkowitch reaction (2 to 3 plus

parent on roentgenograms of the abdomen The non protein nitrog was 244 mg per 100 ml creatinine 11 0 mg per 100 ml and th serum calcium ranged between 10 1 and 11 0 mg per 100 ml Phos phorus ranged between 8 0 and 11 0 mg per 100 ml The alkal n phosphatase was 3 1 to 5 2 Bodansky units The twenty four hour urin volume ranged from 2000 to 3000 cc and contained only 58 to 9 ... appeared and

solitary adenoma of the right lower parathyroid gland ... cm bilateral stag horn calculi and extreme bilateral dilatation of the renal pelvis Microscopically the kidney showed a pseudo-thyroid appearance of the tubules Nephrocalcinosis of the tubules was minimal.

Comment This patient suffered from a potentially reversible type of renal insufficiency and might have been salvaged by early diagnosis and proper treatment The diagnosis and treatment of hyperparathyroidism three years previously probably would have been lifesaving The preterminal biochemical picture illustrates the suppression of the biochemical manifestations of hyperparathyroidism by superimposed renal insufficiency Even the twenty four

Primary hyperparathyroidism, hyperchloremic acidosis, and chronic pyelonephritis constitute by far the most frequent causes of nephrocalcinosis and renal insufficiency (fig 9)

Hyperparathyroidism versus the "Milk Alkali" *(Burnett's) Syndrome*

The syndrome of alkalosis and renal insufficiency resulting from the vomiting of chlorides and the prolonged ingestion of milk and soluble alkalies in intractable peptic ulcer patients has appeared sporadically[34, 41, 166, 268] in the literature since first described by Hardt and Rivers [145] In some of these patients only a transient, reversible renal insufficiency developed, while in others, generalized calcinosis with metastatic calcification of kidneys and other vital organs resulted and a fatal uremia was not infrequent Burnett and his associates[49] reported six cases of a syndrome which they attributed to the prolonged intake of milk and alkalies in the treatment of ulcer, characterized by 1) hypercalcemia without hypercalciuria or hypophosphatemia 2) generalized metastatic calcinosis 3) ocular lesions and 4) renal insufficiency

Since Kirsner, Palmer, and Humphreys[178, 179] and others[237] have shown that intense alkalosis alone does not produce permanent renal damage in either experimental animals or human subjects, it seems probable that other pathogenetic factors such as latent subclinical kidney disease, must be associated with chronic alkalosis to produce this syndrome

Sanderson[300] administered 140 grams of sodium bicarbonate and three liters of milk daily for three weeks to a male ulcer patient Although this tremendous amount of bicarbonate produced a rise of plasma, CO_2 combining power to 40 mEq per liter, a weight gain of nearly 7 kilograms and mild edema of the ankles, the blood urea nitrogen remained unchanged until the end of the period of alkali administration when the level rose slightly In 21 other experiments on human subjects using smaller doses of alkali similar results were obtained No evidence of renal damage was observed Sanderson[300] concluded that man is well able to cope

nosed about three times as frequently as nephrocalcinosis When nephrocalcinosis is detected by roentgenogram examination, the cause can be determined clinically in most instances The cause of urinary calculi, however, is not as easily discernible Contrary to

quate treatment with alkali of patients with nephrocalcinosis secondary to hyperchloremic acidosis Because of the potential reversibility of nephrocalcinosis and the dire consequences of allowing the condition to progress or remain untreated, Mortensen[256] has outlined the diagnostic procedures necessary to establish, in most instances, the precise cause of nephrocalcinosis

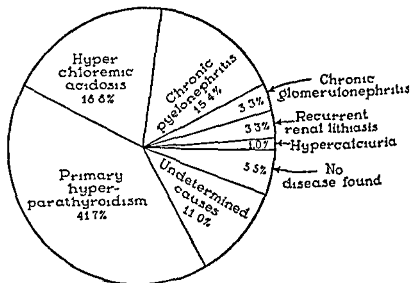


Figure 9 Distribution of causative disorders responsible for roentgenographically demonstrable nephrocalcinosis in 91 collected cases (MORTENSEN JD EMMETT, J L AND BAGGENSTOSS A H Clinical aspects of nephrocalcinosis Proc Staff Meet Mayo Clinic, 28 305, 1953)

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with an enormous alkali intake for periods up to three weeks In one patient suffering from a duodenal ulcer and pyloric obstruction, Sanderson[320] observed that the severe alkalosis resulting from the administration of bicarbonate actually lowered the blood urea nitrogen, whereas vomiting which produced dehydration and a relatively trival alkalosis resulted in a substantial rise in blood urea nitrogen From this observation, Sanderson[320] reasoned, and we concur, that the renal damage associated with clinical alkalosis is more likely due to dehydration and consequent renal ischemia than to alkalosis per se (fig 10) The hypopotassemia associated with alkalosis undoubtedly augments this renal disturbance The profound effects of dehydration and alkalosis on renal function are illustrated in the following case

CASE REPORT

The patient, a twenty six year old white female and known alcoholic addict for many years entered Cook County Hospital on February 4 1949, in a semistuporous condition from continuous vomiting and dehydration The blood pressure was 140/90, pulse 112 and respirations 28 The liv
The bioch
alkalosis
hematocrit was 30 The patient was oliguric (less than 100 cc. of urine in twenty four hours for two days) Despite dehydration the urine specific gravity was 1 010 A trace of albumin was present, but no formed elements were visible microscopically in the urinary sediment. Large quantities of saline solution and 1/6 M sodium lactate were administered intravenously, and the biochemical picture converted to metabolic acidosis with a CO_2 combining power of 9 5 mEq per liter The patient, as a result of this treatment, became overhydrated (hematocrit 21) An intense diuresis obtained, but electrolyte and water balance were ultimately established The non protein nitrogen at the height of the electrolyte disturbance and dehydration was 107 mg per 100 ml, and the creatinine was 5 8 mg per 100 ml The patient recovered, and the azotemia subsided completely

Comment This case illustrates the untoward effects of metabolic alkalosis and dehydration on renal function The extent of the preexisting renal damage, as in most instances, cannot be

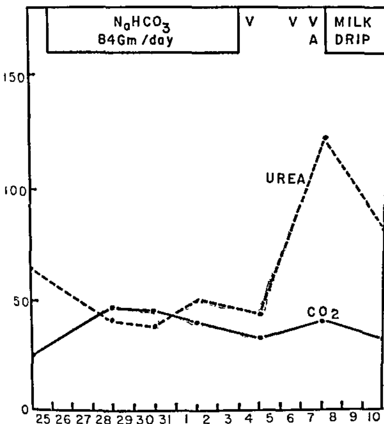


Figure 10 Blood urea (mg /100 ml) and plasma total CO_2 (mEq /L.) in a man with pyloric stenosis receiving 1000 mEq per liter (84 gm) of sodium bicarbonate daily On the days marked with a 'v' the subject vomited 'A' represents the aspiration of over a liter of gastric contents Administration of bicarbonate caused severe alkalosis but lowered the blood urea, vomiting caused a relatively trivial alkalosis but a marked rise in blood urea (SANDERSON, P H Renal response to massive alkali loading Ciba Foundation Symposium on the kidney Boston, Little Brown & Co., 1954)

ascertained Because of the combination of liver disease and renal insufficiency, this case could be classified loosely as hepato renal syndrome, a term which we believe should be dropped from med ical terminology

Ogle and Harvey[274] observed that even when alkalosis results from massive alkali therapy of peptic ulcers, it is seldom accom panied by hypercalcemia The reason only an occasional patient develops hypercalcemia under these circumstances remains obscure

We have observed that when a patient afflicted with latent or subclinical hyperparathyroidism develops an intractable peptic ulcer which is treated with large quantities of milk and alkalies (particularly calcium salts) and alkalosis and azotemia result the clinical and biochemical picture is indistinguishable from the syndrome which Burnett and his associates[49] attributed to the pro longed ingestion of milk and alkali alone The diagnostic dilemma is further compounded by the added complication of frequent and massive gastrointestinal bleeding resulting in shock and renal ischemia With the appearance of peptic ulcer complications and renal insufficiency in the hyperparathyroid patient a clear-cut separation from the milk alkali syndrome becomes a most perplex ing problem *In short the symptoms and findings of peptic ulcer, gastrointestinal hemorrhage, alkalosis, and renal insufficiency often mask the clinical and biochemical manifestations of hyperpara thyroidism*

Whereas in hyperparathyroidism a tendency exists toward hy percalcemia and hypophosphatemia in renal insufficiency the phosphate level is elevated and the calcium depressed With an adequate intake of calcium x ray evidence in bone of hyperpara thyroidism may also be obscured The polyuria resulting from tubular dysfunction and loss of concentrating ability may produce only a weakly positive or negative Sulkowitch reaction Thus the only biochemical proof of the existence of hyperparathyroidism may be the increased twenty four hour excretion of calcium while the patient is on a low calcium diet, and even this clue may be lacking in certain patients (fig 11)

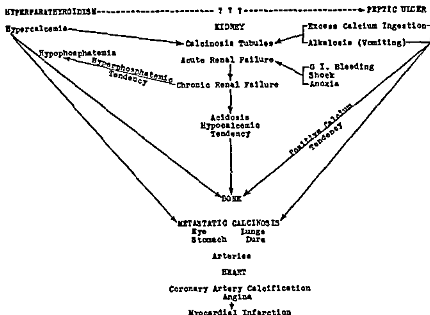


Figure 11 The modification of hyperparathyroidism by peptic ulcer complications and renal insufficiency The usual osseous alterations of hyperparathyroidism as visualized in roentgenograms of bone are negated by the additive effects of excess calcium ingestion (milk and calcium salts) and the alkalosis of chloride depletion from vomiting Alkalosis causes a shift of ionized calcium to protein bound calcium and also reduces the solubility of calcium salts The latter effect counteracts the tendency of hyperparathyroidism to mobilize calcium from bone Chronic renal insufficiency which tends to produce acidosis phosphate retention and hypocalcemia further modifies the biochemical picture of hyperparathyroidism (ATLAS D H, GABERMAN, P, AND EISENBERG, H L. Syndrome of masked hyperparathyroidism Ann Int Med 44 1195–1210 1956)

CASE REPORT

B O, a forty five year old white male married bookkeeper, was first admitted to Mount Sinai Hospital on March 15, 1947, with a twenty five year history of intractable ulcer symptoms manifested by the pain food relief sequence During this twenty five year period, he ingested large quantities of milk and cream and soluble alkalies For the past

because
and in
)ne year
previously, he was seen by a gastroenterologist was told he had symptoms of an obstructive ulcer, and was advised to undergo surgery During the month before hospitalization, he frequently passed black stools For two days prior to admission, he often induced vomiting and took large doses of alkalies to relieve his ulcer pain

Physical examination disclosed an apprehensive, thin pale, dehydrated, and chronically ill white male complaining bitterly of weakness, thirst and burning epigastric pain relieved only by self induced vomiting His blood pressure was 100/70, pulse 130, and temperature 98 0 F

By slit lamp examination, small subepithelial deposits were noted bilaterally adjacent to the limbus and extending two to three millimeters into the cornea at the interpalpebral zone The eyes were otherwise not remarkable Loud, blowing Grade II, systolic murmurs were audible at the apex and base of the heart No other abnormalities were found in the chest Slight epigastric tenderness was elicited The red blood cell count was 2 700 000, hemoglobin 7 5 grams and the white blood count was 17,200 with a normal differential distribution The hematocrit was 21 There was oliguria for three days Severe azotemia and metabolic alkalosis were reported He was placed on a Meulengracht regimen

Electrolyte and fluid balance was established by the administration of intravenous glucose and saline solutions A satisfactory urine flow was obtained, the azotemia was precipitously reduced, and his general condition rapidly improved Urinalysis disclosed little of significance
of the

stro
intestinal hemorrhage, dehydration and alkalosis A gastric resection was advised but was refused by the patient He was discharged on April 19, 1947 improved

Second Admission—December 14, 1947

The chief complaints now
breath His temperature was
lobe pneumonitis was reporte
therapy, became afebrile, and the lungs cleared within a few days Severe azotemia with a non protein nitrogen of 136 mg per 100 ml

and creatinine of 7 4 mg per 100 ml was reported on admission He

for relief of ulcer pain

Third Admission—August 4, 1948

The patient complained of weakness, shortness of breath, and the

Fourth Admission—January 17, 1949

The complaints were similar to those on previous admissions with the addition of painful spasm of the calf muscle and a generalized pruritus The level of azotemia and anemia were unchanged A depression of serum chloride was noted which could not be elevated by large amounts of orally administered sodium chloride The diagnosis of salt losing nephritis was suggested He was discharged on January 27, 1949

Fifth Admission—March, 3, 1949

He entered the hospital because of weakness, hematemesis, and melena His red blood cell count was 2 000,000 and the hemoglobin 6 8

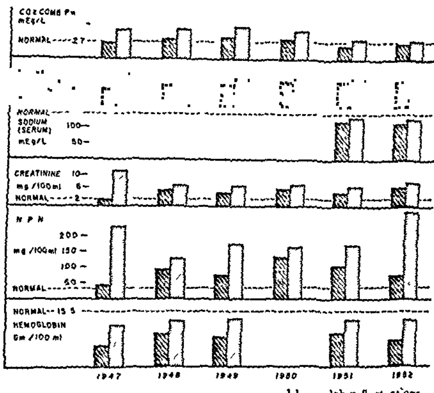
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Sixth Admission—October 12, 1949

The complaints were essentially unchanged On this admission the CO_2 combining power was found to be 45 4 mEq per liter, and hyponatremia and hypochloremia were again noted in addition to the azotemia Treatment consisted of blood transfusions and electrolyte therapy He was discharged slightly improved on November 5, 1949



the lumina of these vessels were greatly reduced The iliac arteries presented similar changes

The *kidneys* were moderately enlarged, weighing 280 grams together On their external surface there were multiple cysts measuring up to 1 5 cm containing straw colored fluid The renal capsule was firmly attached to the cortex which was finely granular The thickness of the cortex was considerably reduced, and there were numerous yellowish-

the *lungs* and *calcification* of the cartilaginous plaques of the trachea and large bronchi. The other viscera were grossly *normal* except for slight enlargement of the parathyroids and *calcification* of the dura over the convexity of the cerebrum.

Microscopic examination confirmed the visceral changes described above. In addition to the healed posterior wall infarct of the myocardium there were areas of recent myocardial necrosis. *Numerous* foci of calcification were seen within the infarcted regions. A large coronary artery was completely occluded by a partly calcified hyaline-like thrombus. The lungs displayed areas where the alveoli were obliterated by proliferating fibrous connective tissues containing calcium, which in some areas showed osteoid metaplasia. There was *moderate* arteriosclerosis of the branches of the pulmonary artery. Numerous glomeruli were completely hyalinized. Some tubules were atrophic, *while* others showed partial necrosis of their epithelial lining. The adjacent interstitial *regions* contained masses of purplish, amorphous material which gave the staining reactions of *calcium* (fig. 13). There were infiltrating lymphocytes throughout the interstitial tissue *of the* kidneys. The branches of the renal arteries showed severe arteriosclerosis. Sections of the *parathyroids* revealed diffuse hyperplasia with predominance of large polygonal water-clear cells. In one parathyroid there was *a well encapsulated nodule* measuring 1.5 × 2 cm., composed of small dark-staining cells arranged in cords *and* tall cuboidal cells with a tendency to form acini (fig. 14); these cells had a clear cytoplasm. *The* stroma was scant and richly vascularized. The marrow of the vertebrae was partially replaced by fibrous connective tissue. The bony trabeculae were atrophic and some were surrounded by osteoclastic giant cells (fig. 15). Sections of the dura revealed large foci of calcification with metaplastic bone formation.

An eyeball was examined grossly and histologically by Dr. Gerald B. Kara (New York Eye, Nose and Throat Infirmary). *The* anatomical diagnoses of the ocular pathology were: 1) band-form keratitis, 2) glaucoma, 3) calcified plaques in sclera, 4) chronic choroiditis, 5) uveal atrophy, 6) uveal and retinal vascular sclerosis, 7) gliosis of retina, 8) optic atrophy.

The *anatomic diagnoses* were as follows: 1) solitary adenoma of the parathyroids with diffuse hyperplasia; 2) nephrocalcinosis superimposed on a chronic pyelonephritis and bilateral congenital polycystic kidneys (mild); 3) pyelitis cystica; 4) osteitis fibrosa; 5) metastatic calcification of the iliac arteries, trachea, lungs, dura mater; 6) severe calcific sclerosis of the coronary arteries with thrombotic occlusion; 7) hyper

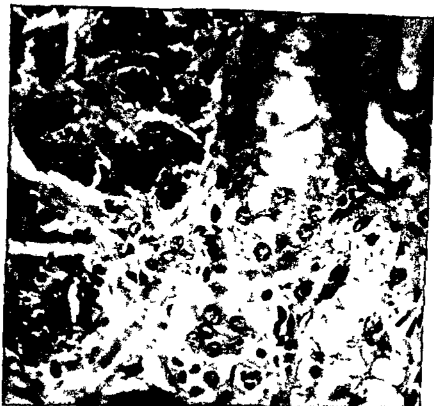


Figure 13 Renal tubules showing partial necrosis and deposition of calcium × 880 (ATLAS D H GABERMAN P AND EISENBERG H L Syndrome of masked hyperparathyroidism Ann Int Med 44 1195 1210 1956)

trophy of the heart with recent and old myocardial infarct 8) organized bronchopneumonia 9) chronic peptic ulcer at margin of gastroenterostomy healed peptic ulcer at the pylorus

Discussion The intense deterioration of renal function produced by each episode of hematemesis shock alkalosis and dehydration demonstrates the vulerability of previously impaired kidneys to these deleterious influences A considerable degree of reversibility however resulted from restoration of blood volume



Figure 11 Parathyroid adenoma Fibrous capsule separates adenoma from normal parathyroid tissue × 190 (ATLAS, D H GABERMAN P AND EISENBERG H L Syndrome of masked hyperparathyroidism Ann Int Med 44 1195–1210 1956)

and water and electrolyte balance This susceptibility of kidneys with underlying disease to disturbances of circulation, water and electrolyte balance has been previously noted [121] In our patient, it is probable that insidious hyperparathyroidism produced calcinosis of the tubules which then became vulnerable to alterations of the internal milieu The congenital cysts and interstitial pyelonephritis



Figure 15 Marrow obtained from vertebra showing osteitis fibrosa, fibrosis of marrow, and osteoclastic activity × 880 (VILAS, D. H., GABERMAN, P., AND EISENBERG, H. I.: Syndrome of masked hyperparathyroidism. Ann. Int. Med. 44: 1195–1210, 1956)

were of minor consequence and probably played an insignificant role in the sequence of events which culminated in renal failure.

The occasional normal serum calcium, the elevated serum phosphorus, the normal alkaline phosphatase, the absence of a strong Sulkowitch reaction, and the failure of bone roentgenograms to disclose osteitis fibrosa cystica diverted us from the diagnosis of

primary parathyroid disease Unfortunately the crucial and diagnostic quantitative determination of calcium excreted in twenty four hours on a low calcium diet was not done It should be noted however that hypercalciuria may not be detected by the Sulkowitch

[illegible] parathyroidism is associated with

[illegible] of poly

[illegible] retention

[illegible]

phosphaturia of hype [illegible] to

obscure hyperparathyroidism may be absent

While this patient was on our service the report by Burnett et al [19] appeared and at the time the findings in our patient seemed compatible with their description

Review of the "Milk Alkali" (Burnett's) Syndrome [19]

We believe that a critical review of the various cases reported as Burnett's[19] syndrome may dispel some of the present confusion connected with this problem (table 4)

The most recent and by far the most comprehensive review of [illegible] Wenger Kirsner and Palmer [illegible] with

peptic ulcer hospitalized [illegible] 1956

[illegible] ted to patients studied in detail [illegible] chem

[illegible] 1) adequate in

[illegible] ent of peptic ulcer

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gen determinations [illegible]

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[illegible]

calcification

Carpenter and Butler reported a case of a twe [illegible] ld male who demonstrated six of the nine criteria of Burnett's syn

drome The patient did not manifest the criteria in the following three ways 1) there was a tendency to acidosis rather than alkalosis 2) there was no clinical improvement on a low calcium diet, and 3) no history was obtainable of an excess intake of absorbable alkali In as much as hyperparathyroidism could not be eliminated, surgical exploration of the neck was performed, but no parathyroid adenoma was found The patient died in uremia The antemortem clinical diagnosis was Burnett s syndrome, chronic pyelonephritis, renal acidosis and parathyroid hyperplasia At autopsy, surprisingly, a large functioning parathyroid adenoma was discovered in the superior mediastinum Thus Carpenter and Pautler[50] concluded that in most instances the Burnett s syndrome is primary hyperparathyroidism complicated by an excessive intake of milk and absorbable alkali

McQueen[239] applied the terms milk poisoning and calcium gout in his report of a patient whose symptoms conformed to the criteria of Burnett *et al*[49] This patient presented excruciatingly painful exquisitely tender swelling of a joint, striking in resemblance to acute gout The pain would reach a peak within a few hours and then subside only to recur in another joint area While admitting that hyperparathyroidism could not be excluded without determinations of calcium excretion McQueen[239] in our opinion incorrectly concluded that the diagnosis of hyperparathyroidism was unlikely because of the absence of skeletal changes and the normal serum alkaline phosphatase after restriction of calcium intake He made the interesting observation, with which we concur, that the development of Burnett s syndrome may not be possible in the absence of preexisting renal disease

Kyle[148] in a report of two cases pointed out the extreme difficulties involved in the differentiation of hyperparathyroidism from the milk alkali syndrome In one of his patients excessive intake of milk alkali was the major problem in another, a parathyroid adenoma was surgically removed Postmortem examination of the first patient disclosed a congenital horse shoe kidney with marked hydronephrosis extremely severe nephrocalcinosis and diffuse inter

stitial nephritis apparently secondary to the calcinosis Metastatic calcification was demonstrable in the dura lungs orbits and medium sized arteries A large ulcer crater was present in the first portion of the duodenum It was apparent that the patient died of renal failure Since the parathyroid glands were not isolated after diligent dissection of the neck the possible existence of a small functioning parathyroid adenoma was not entirely eliminated In the second patient removal of a parathyroid adenoma resulted in a complete clinical cure It is noteworthy that in the latter patient notwithstanding the hypercalcemia the twenty four hour urinary excretion of calcium was not usually increased Kyle[1 9] suggested the possibility that this hypercalcemia without hypercalciuria may be due to the interference of the urinary excretion of calcium by alkalosis

Kyle[188] offered one important differential diagnostic feature of the true Burnett s syndrome namely improvement on a diet low in calcium and absorbable alkali He stated that with proper dietary restriction patients with hyperparathyroidism should demonstrate sufficient improvement in renal function to uncover the characteristic laboratory features of this disease *unless irreversible renal damage has occurred under which circumstances differentiation of these two disorders may depend on surgical exploration and examination of the parathyroids* Kyle[199] did not subscribe to the opinion expressed by Carpenter and Pautler and the authors[1] who doubt that Burnett s syndrome can develop in the absence of previous renal damage or obscure hyperparathyroidism

Schneider[3 5 8 6] related that under certain circumstances Burnett s syndrome and hyperparathyroidism may be indistinguishable He presented two illustrative case histories In the first patient the symptomatology led to surgical exploration of the neck and later of the mediastinum No parathyroid tumor or hyperplasia was found and discontinuance of milk and absorbable alkali resulted in prompt correction of hypercalcemia and azotemia Although this patient was regarded as having had Burnett s syndrome the presence of a persistent albeit improved urea clearance suggests to us that this patient may have had preexisting latent tubular damage

which made the kidney vulnerable to alkalosis In other words the impaired nephrons were unable to properly regulate the internal milieu or manage an overwhelming alkali or calcium load The second patient presented a similar clinical and biochemical pattern which was corrected by surgical removal of a parathyroid adenoma Schneider[3,6] nevertheless concluded that Burnett s syndrome may be a distinct clinical entity and not necessarily a manifestation of hyperparathyroidism[3] He and his associates regard a low serum phosphorus level as a most reliable clue to the diagnosis of hyper parathyroidism unless renal insufficiency has occurred

Schneider[3] described a third patient with diabetes mellitus and long standing duodenal ulcer in whom the milk alkali syndrome developed rapidly following a diet of milk and calcium chloride powders for eight days The level of non protein nitrogen rose from 39 to 143 mg per 100 ml and the patient became stuporous and had polyuria and polydipsia The serum calcium rose to 16 5 mg per 100 ml With institution of a low calcium diet the serum calcium level and renal function returned to normal Since urinary calcium excretion was not reported in the protocol the existence of hyper parathyroidism was not completely eliminated

Scholz and Keating[3,7] in a review of eight cases which they classified as milk alkali syndrome considered antecedent renal damage important in the production of this syndrome They also noted the difficulty involved in the differentiation of this syndrome from primary hyperparathyroidism without bone disease partic ularly in a patient who develops an active ulcer and renal insuf ficiency

They cited the case of a fifty one year old white male with symp toms and findings of bleeding ulcer excessive ingestion of milk and alkalies azotemia hypercalcemia and hypercalciuria over a twenty eight year period which led to the consideration of either hyper parathyroidism or Burnett s syndrome The neck was surgically ex plored but no parathyroid tumor was found The patient refused surgical exploration of the mediastinum Because of recurrence of ulcer symptoms a gastrectomy and duodenectomy were performed

with an uneventful postoperative course Prior to discharge the blood calcium and phosphorus levels were reported to be normal According to the authors the final diagnosis in this patient is still open to question

Hyperparathyroidism Complicated by Peptic Ulcer and Gastrointestinal Bleeding

To further compound the diagnostic difficulties patients suffering from primary hyperparathyroidism with intractable peptic ulcer often develop gastrointestinal hemorrhage

It is noteworthy that *most of the cases reported as Burnett s syndrome as well as our patient suffered recurrent gastrointestinal hemorrhage* resulting in shock and anemia One would reason therefore that shock and renal ischemia contribute considerably to the tubular damage and the renal insufficiency which is apparent in these patients

Wenger Kirsner and Palmer[403] also suggest that gastrointestinal hemorrhage seems to be an important factor in the genesis of renal insufficiency presumably because of the hemodynamic changes induced in the kidneys Eight of their 35 cases of milk alkali syndrome had moderate gastrointestinal hemorrhage immediately preceding the hypercalcemia

St Goar[36] in a review of 45 proven cases of primary hyperparathyroidism also directed attention to gastrointestinal symptoms as a diagnostic clue Unexplained vomiting was present in nine of the 45 patients Four of these patients (8 8 per cent) had peptic ulcer In another series the same incidence of gastrointestinal symptoms (12 out of 137) was reported by St Goar He concluded that unexplained nausea vomiting anorexia abdominal pain weight loss and intractability of peptic ulcer should lead to a consideration of hyperparathyroidism He pointed out that although the biochemical osseous and renal manifestations are of comparatively greater significance an awareness of the more obscure gastrointestinal symptoms is important to achieve early diagnosis at a time when reversibility is possible

which made the kidney vulnerable to alkalosis In other words the impaired nephrons were unable to properly regulate the internal milieu or manage an overwhelming alkali or calcium load The second patient presented a similar clinical and biochemical pattern which was corrected by surgical removal of a parathyroid adenoma Schneider[36] nevertheless concluded that Burnett s syndrome may be a distinct clinical entity and not necessarily a manifestation of hyperparathyroidism He and his associates regard a low serum phosphorus level as a most reliable clue to the diagnosis of hyper parathyroidism unless renal insufficiency has occurred

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hemorrhage are particularly prone to develop hypochloremic alkalosis

Albright and Kerr reported a case of duodenal ulcer associated with hyperparathyroidism due to primary hyperplasia of the parathyroid glands The patient suffered one episode of massive hematemesis They [8] too emphasized the frequent coexistence of hyperparathyroidism and duodenal ulcer and reported a 14 per cent (4 cases) incidence of duodenal ulcer in 28 cases reviewed by them of primary hyperplasia of the parathyroid glands They believe that the administration of milk and alkalies to patients with hyperparathyroidism and duodenal ulcer may precipitate parathyroid poisoning with nausea vomiting, lethargy prostration and azotemia which can be fatal

Agna and Goldsmith[1] faced a dilemma with two patients in whom primary hyperparathyroidism was associated with intractable peptic ulcer In both instances there was considerable delay in arriving at the correct diagnosis for the clinical picture was that of peptic ulcer associated with gastrointestinal symptoms of twenty years duration Both patients had a gastric resection before hyperparathyroidism was recognized and corrected

The precise mechanism of the association of hyperparathyroidism with peptic ulcer is obscure [8] Schiffrin[3 3] has demonstrated an intimate relationship between the parathyroid gland and gastric function in dogs i e the administration of parathyroid hormone increased the volume acidity and chloride concentration of the gastric secretions

Ocular Lesions

Two distinct types of ocular lesions have been described in hyperparathyroidism and other hypercalcemic states One is calcification of the eyeball recognizable only by special bone free roentgenological techniques as described by Fleischner and Shalek [11] and the other is the corneal and conjunctival deposits which may require slit lamp for identification but occasionally can be detected with aid of an ordinary pocket light

Gutman[139] appears to have been the first to emphasize the fact that the gastrointestinal symptoms of hyperparathyroidism may so dominate the symptomatology that peptic ulcer is suggested Rogers *et al* [308, 309] reported three autopsied cases of primary hyperparathyroidism associated with peptic ulcer in which the gastrointestinal symptoms during life were presumed entirely due to ulcer

Black[33] noted that twenty four per cent of patients with hyperparathyroidism have clinical evidence of peptic ulcer at one time or another and an additional fifteen to twenty per cent of these patients have some ulcer like symptoms without demonstrable x ray evidence of ulcer *He suggested screening of patients with intractable ulcer symptoms for evidence of hyperparathyroidism* Black[33] also suggested that the peptic ulcer symptoms associated with hyperparathyroidism respond poorly to medical and surgical treatment until the hyperparathyroidism is cured whereupon they become more amenable to ulcer therapy

Schneider and Robinette[3] • reported a similar experience This relationship of hyperparathyroidism to ulcer has also been noted by Snapper[356] as well as Howard and his associates[160] who commented upon the high incidence of peptic ulcer in patients with hyperparathyroidism (15 per cent in the Johns Hopkins group) Becker and his group[74] studied a large series of autopsy records of patients with the anatomic diagnosis of chronic active or healed duodenal ulcer regardless of the cause of death They eliminated conditions associated with a high incidence of renal calcification (hyperparathyroidism hypervitaminosis D metabolic bone disease chronic renal failure etc) Their study indicated that nephrocalcinosis occurred more frequently (36 per cent) in the presence of duodenal ulcer than in other medical conditions (13 per cent) A significantly higher incidence of nephrocalcinosis was reported in those patients whose symptoms required alkali therapy and surgical intervention They concluded that the syndrome of alkalosis and renal insufficiency is probably largely due to dehydration and hemoconcentration rather than hyperalkalinization alone They also observed that patients who develop massive gastrointestinal

nasal or temporal side or both [59] These deposits are most dense at the periphery and diminish centrally but may involve almost the entire cornea The latter type of calcification resembles but is distinct from band keratitis which may also be associated with hypercalcemic states [61] All types of ocular lesions resulting from hypercalcinosis have been reported to improve after correction of the calcium disturbance

Diffuse generalized calcification of the cornea with opacification and visual impairment due to hypercalcemia was first reported in a patient with sarcoidosis by Cogan and Henneman [60] In addition to mild renal insufficiency (non protein nitrogen 53 mg per 100 ml) and diabetes mellitus the patient gave a history of prolonged ingestion of a multivitamin preparation containing 1000 units of vitamin D No history of ulcer or excessive ingestion of milk was elicited Detailed metabolic studies have not yet been reported in this patient but prolonged steroid and sodium phytate therapy resulted in restoration of normal serum calcium levels and clearing of the corneal calcification (fig 17 A and B)

Cogan and Henneman[8] emphasized the practical importance of the early recognition of corneal manifestations of hypercalcemia at a time when reversibility is still possible They further emphasized that advancing renal insufficiency with attending phosphate retention may suppress hypercalcemia so that the corneal lesions may be the only clue to the underlying condition

Specific ophthalmological examination for calcium deposits was made in fifteen patients with milk alkali syndrome by Wenger Kirsner and Palmer[4] Definite abnormalities probably due to calcium salt deposits were observed in six of whom only three had bilateral conjunctival infiltrates In none of the patients was the diagnosis confirmed by biopsy examination

Roentgenographic Evidence of Hypercalcemia

Increased density of the skull and long bones and calcification of the periarticular tissues tendons medium sized arteries skin dura and kidneys were noted on roentgenogram examination of a num

Walsh and Howard[30] reported this distinctive phenomenon in the eyes of one half of their patients with hypercalcemia. They believe these lesions are the direct result of hypercalcemia and enable the physician to recognize hypercalcemia at the bedside (fig 16).

The conjunctival deposits appear as minute, clear, glass-like particles in the region of the palpebral fissures. The corneal type of deposits appear as grayish, granular, epithelial and subepithelial opacities which form concentrically at the limbus on either the



Figure 16. Concentric calcific deposits in cornea of patient with hypercalcemia due to multiple myeloma. Total serum calcium 16 mg per 100 ml. (Medical Illustration Service, Veterans Administration West Side Hospital, Chicago 12, Illinois.)

ber of hypercalcemic patients reported as atypical hyperparathyroidism or its facsimile Burnett's syndrome (table 4) Several factors are operative in this precipitation of calcium 1) increased CO_2 content and alkalinity of the blood 2) decreased plasma protein of the blood 3) increase in quantity and alterations of the composition of calcium salts Wells[409] has termed the deposition of calcium within tissues where it is not normally found metastatic calcification The so called acid secreting organs (lungs stomach and kidney) are especially vulnerable to metastatic calcification

Conclusions

It is apparent that ocular lesions bone changes generalized calcinosis nephrocalcinosis hypercalcemia without hypophosphatemia and renal insufficiency are not specific for either the milk alkali syndrome or hyperparathyroidism but are commonly associated with many conditions producing hypercalcemia

Kyle[188] related that his data as well as the data of Burnett and his associates indicated that *No single feature of the milk-alkali syndrome is completely dependable in ruling out hyperparathyroidism* He further observed that Only the sequence of change that follows correction of the abnormal diet is truly helpful, and in some cases diagnosis may depend on surgical exploration Since Carpenter and Pruitt[37] Kyle[188] Schneider[3,5,8,6] and the authors[17] have described patients who demonstrated most of the features outlined by Burnett[39] but were ultimately proven to have had hyperparathyroidism *it is our firm belief that the majority of cases reported in the literature as Burnett's syndrome are in all probability cases of occult hyperparathyroidism* A possible exception may be a small group of patients with previously undetected latent renal disease who developed peptic ulcer symptoms which are treated with excessive quantities of milk calcium salts and other alkalies Under these circumstances it is conceivable that the syndrome of Burnett can develop in the absence of hyperparathyroidism This concept is supported by the observations of



Figure 17 Appearance of the right eye when the patient was first seen (A) and two years after the beginning of oral treatment with cortisone and sodium phytate (I —
diffuse granular o
white spot in the
flash light and serves to demonstrate the smoothness of the anterior surface The cornea cleared almost completely as the blood calcium returned to normal (B) (COGAN D G AND HENNEMAN P H Diffuse calcification of the cornea in hypercalcemia New England J Med 257 451–453 1957)

several cases presenting a symptom complex strikingly similar to that of our own patient Sawyer and Solez[372] reported a case of salt losing nephritis simulating adrenal cortical insufficiency in a fifty three year old white male with a recurrent obstructing and bleeding peptic ulcer of seven years duration The non protein nitrogen rose to 319 mg per 100 ml following a prolonged episode of vomiting and bleeding As in our case the azotemia was improved by transfusions and intravenous administration of electrolyte solutions Four months later he expired during a similar episode Necropsy disclosed severe nephrocalcinosis and generalized metastatic calcinosis No bone disease was found *No mention is made of examination of the parathyroid glands* However the authors stated *The extensive deposits of calcium in other tissues pointed to a more general metabolic dyscrasia* The cause of this was open to speculation They observed hyperthrophy of the adrenal cortex which they speculated represented a compensatory attempt to stimulate the renal tubules into retaining salt

Murphy *et al*[263] reported four cases of salt losing nephritis One of their cases was a fifty three year old white male with a long standing ulcer history who had taken large quantities of alkalies He too suffered an episode of vomiting and gastrointestinal bleeding resulting in alkalosis hypochloremia hyponatremia and augmentation of azotemia This patient was discharged improved on oral sodium chloride therapy

Knowles *et al*[182] reported a case of salt losing nephritis in which the composition of the urine was consistently uniform both with regard to excretion of electrolytes and total solutes The patient was a 37 year old white male who gave a history of twelve years of persistent ulcer pain requiring medical treatment The details of therapy were not given in the protocol During this period he had symptoms of nausea and vomiting after meals The blood pressure was more than 120/80 and pigmentation of the skin was noted The conjunctivae showed no abnormalities The blood urea nitrogen ranged from 61 to 200 mg per 100 ml creatinine 9 2 to 17 1 mg per 100 ml, sodium 120 to 145 mEq /L. chlorides 79 to

Wenger Kirsner and Palmer[403] Sixteen of their 35 patients with milk alkali syndrome had a definite history of preexisting hypertension Of their entire series in only one patient did the milk alkali syndrome develop without obvious predisposing cause and even this single patient gave a past history of scarlet fever As observed by Kyle[188] *There is absolutely no evidence that the milk alkali syndrome could develop in the absence of pre existent renal impairment* Wenger Kirsner, and Palmer[401] also concluded that decreased renal function is an important factor in the genesis of the milk alkali syndrome whether the impairment results from pre existing hypertension renal disease dehydration alkalosis or gastrointestinal hemorrhage

Salt Losing Nephritis

Cheyne and Whitehead[58] reported a case of salt losing nephritis recently termed Thorne s syndrome by Enticknap[87] which they attributed to excessive ingestion of alkalies and intractable vomiting These authors observed that while only a few cases of salt losing nephritis are recorded the incidence of those patients with a history of excessive alkali therapy is high and therefore suggests that such therapy must be considered one of the possible causes of this interesting tubular defect

In our patient with masked hyperparathyroidism we observed for a considerable time a marked depression of the serum sodium and chloride level which could not be elevated by the oral or intravenous administration of large quantities of sodium chloride The adminstered sodium chloride was almost quantitatively excreted in the urine During this stage of his illness a diagnosis of salt losing nephritis was considered[390]

The inability of damaged renal tubules to conserve salt has been well known[163] This manifestation of disturbed tubular function frequently appears during the course of any chronic renal disease or even in conditions not primarily renal[43] e g infections[79] or injuries to the brain[290] and certain pulmonary lesions[411]

A review of reported cases of salt losing nephritis disclosed

duce renal insufficiency, it is conceivable that alkalosis contributed to the renal insufficiency in this patient

Relman and Schwartz,[302, 334] in a study of five patients summarized the clinical features of a previously unrecognized disorder of renal function associated with potassium deficiency resulting from chronic diarrhea The syndrome is characterized by severe hypokalemia, absence of dehydration, sodium depletion and other electrolyte disturbances, normal or only slight elevations of the blood urea nitrogen, vasopressin resistant hyposthenuria, minimal changes in the urinary sediment, minimal inconstant albuminuria, striking histologic changes of the tubules (biopsy specimen), and potential reversibility by correction of potassium deficit

Schwartz[335] summarized the current literature on the specific effects of potassium depletion from various causes on tubular epithelium Vacuolization and degeneration of the tubules without changes in the glomeruli have been attributed to potassium depletion from the diarrhea of ulcerative colitis or excessive use of laxatives In patients with renal disease, potassium depletion from vomiting and diarrhea may induce additional renal damage Potassium depletion may be partially responsible for the disturbance of renal function attributed to alkalosis since potassium depletion and alkalosis are frequently concomitant Potassium depletion may also be the cause of renal dysfunction in patients with aldosterone producing adrenal tumors

"Water Losing Nephritis"

The term water losing nephritis was introduced by Roussak and Oleesky[314] in a description of two patients who exhibited a syndrome simulating diabetes insipidus which was unresponsive to the action of pitressin In one patient, myelomatosis, particularly involving the distal tubule, was the cause of the defect and the second patient was found to have hydronephrosis caused by an enlarged prostate gland because of carcinoma The latter patient recovered from polyuria after relief of the urinary obstruction and was able to produce a concentrated urine Sturtz and Burke[369] suggested the

103 mg per 100 ml serum calcium 8 9 to 10 3 mg per 100 ml and phosphorus 3 0 to 8 8 mg per 100 ml The patient died in uremic coma Examination of the parathyroid glands was not mentioned in the autopsy report Each kidney weighed 100 grams and appearance was compatible with chronic pyelonephritis Renal calcification was not reported Quantitative urinary calcium excretion was not recorded The authors noted It is not clear what role the ulcer therapy may have played in the development of pyelonephritis in the current case

Levere and Wesson[198] reported salt losing nephritis in a twenty nine year old white male in whom the diagnosis was confirmed by needle biopsy of the kidney The administration of substantial quantities of sodium chloride and sodium bicarbonate resulted in considerable clinical and biochemical improvement so that the patient was gainfully employed despite a persistent azotemia These authors proposed the following minimal criteria for the diagnosis of salt losing nephritis as distinct from other salt losing states 1) signs and symptoms of dehydration on normal salt intake (5 to 8 gm per day) that can be relieved by an increased salt intake up to 10 to 20 gm per day 2) absence of response to adrenal steroids or presence of such steroids in the urine in normal amounts and 3) persistence on a high salt diet of evidence of renal disease i e *azotemia anemia polyuria low urinary specific gravity*

Potassium Losing Nephritis

Wyngaarden[413] reported a case of malignant hypertension uremia alkalosis and a defect in renal conservation of potassium associated with renal insufficiency In this patient it was established that the potassium deficiency was due to renal loss because hypokalemia and hyperpotassuria were simultaneously present The alkalosis could not be attributed to gastrointestinal losses adrenal cortical hyperfunction ingestion of alkali or use of mercurial *diuretics and therefore was* probably secondary to potassium deficiency Autopsy confirmed the diagnosis of malignant nephrosclerosis producing tubular dysfunction Since *alkalosis can pro-*

duce renal insufficiency, it is conceivable that alkalosis contributed to the renal insufficiency in this patient

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term, 'obstructive water losing uropathy" to describe this condition

Congenital defects of the renal tubules producing a similar syndrome have been reported under the term, "nephrogenic diabetes insipidus"[110] Earley[92] reported a similar case due to obstructive uropathy in a six month old infant ' Water losing nephritis," therefore, is a symptom complex which can result from several diverse conditions and is not a specific disease as the term suggests

Conclusions

Salt losing, potassium losing,[89] and water losing nephritis are terms which we feel are more euphonic than nosologic Renal damage may be of varying degree and character, and the effects on electrolyte balance are unpredictable The kidney may lose or retain sodium, potassium,[90] chloride, phosphate, calcium, amino acids, or water The German workers have termed this erratic behavior of the kidney *"Launisch"*—moody We believe, therefore, that the terms salt losing nephritis, "potassium losing nephritis," and 'water losing nephritis" are not precise and should be discarded A search for specific etiologic factors is necessary for accurate classification

Vitamin D and Irradiated Sterol Intoxication

Renal insufficiency which may be reversible has been observed in vitamin D and/or irradiated sterol intoxication [2] Massive doses of vitamin D have been used in the treatment of rickets, rheumatoid arthritis, various allergic states, osteoporosis of various causes, hypoparathyroidism, tetany, and mal united fractures (in an attempt to enhance bone regeneration) Numerous untoward reactions have been attributed to this group of sterols, i e , nausea, anorexia, vom[illegible] abdominal pain, diarrhea, muscular weakness, [illegible] ences [illegible] were not generally appreciated Since high potency vitamin D preparations have been used indiscriminately and may be purchased freely

over the counter, a history of vitamin D ingestion should be sought in all patients who manifest hypercalcemic symptoms and/or renal insufficiency

The state of vitamin D intoxication can be diagnosed prior to the development of renal insufficiency by observation of metastatic calcification of the joints tendons skin soft tissues eyes and kidneys Diet appears to be an important factor in the genesis of this syndrome since the degree of hypercalcemia resulting from irradiated ergosterol is related to th amount of calcium ingested [57]

In two cases reported by Tumulty and Howard[397] fractures were treated with massive doses of irradiated sterols and milk in addition to the usual prolonged immobilization Thus in these two instances it is probable that several factors were cumulative in the production of renal damage viz prolonged immobilization high calcium diet and administration of irradiated sterols Most workers agree that renal damage can result solely from hypercalcemia Others [159] however hold to the opinion that hypercalcemia to an extreme degree may occur without evidence of kidney damage and therefore hypercalcemia is not necessarily a factor in renal injury associated with irradiated sterol intoxication Danowski and his associates[71] observed two patients with renal damage secondary to massive doses of vitamin D administered for treatment of arthritis These patients showed extensive generalized calcinosis in addition to impairment of renal function but nephrocalcinosis could not be demonstrated on roentgenogram examination

Freedman[114] reported a case of vitamin D intoxication which resulted in hypercalciuria and calculus formation with hypercalcemia This metabolic disturbnce persisted for at least fifteen months after the vitamin was withheld and may therefore have been an example of idiopathic hypercalciuria rather than hypercalciuria from vitamin D intoxication

Chaplin Clark and Ropes[57] reviewed the protocols in the literature of 111 cases of vitamin D intoxication and added detailed information of 7 cases which they studied and treated at the Massachusetts General Hospital They particularly emphasized the

findings of band keratitis and metastatic calcium cysts They outlined the syndrome as follows

1 *General* weakness, fatigue, weight loss
2 *Gastrointestinal* nausea, vomiting, diarrhea, abdominal cramps
3 *Neurological* headache, paresthesias, vertigo
4 *Psychiatric* variable mental symptoms—depression, mild psychosis, stupor
5 [illegible]
6 [illegible] ive
7 [illegible]
8 *Chemical* elevated serum calcium and phosphorus, with normal or slightly elevated alkaline phosphatase Progressive nitrogen retention
9 *Roentgenological* diffuse demineralization of the bones in advanced cases periarticular soft tissue calcifications
10 *Pathological* scattered calcium deposition in kidney, blood vessels, periarticular soft tissues, heart, stomach, lung, thyroid, and pancreas

Renal biopsy on a patient with vitamin D intoxication resulting from the administration of calcium and ergosterol concentrates for the treatment of hypoparathyroidism revealed considerable calcium deposits in the collecting tubules which were not discernible on roentgenogram examination [165]

In this connection it is of interest to note that Mortensen *et al*,[256] in reviewing 48 cases from the literature and 43 additional cases from the Mayo Clinic, observed that although conditions such as vitamin D intoxication, multiple myeloma, osteolytic metastasis and chronic obstruction of the upper portion of the gastrointestinal tract with vomiting prolonged ingestion of alkalies, and mercuric poisoning are listed as well known causes for nephrocalcinosis in standard textbooks none of these conditions was encountered in their series

CASE REPORT

The patient, a sixty year old female housewife, entered three different hospitals during a six month period The first hospital admission was

on April 26, 1955, because of recurrent episodes of epigastric pain radiating to the right scapular region associated with nausea and vomiting of three years duration The blood urea nitrogen was 31 mg per 100 ml, and the urinalysis disclosed no abnormalities The presence of cholelithiasis was confirmed by roentgenograms, as was a calcific density over the lower pole of the left kidney A cholecystectomy was performed and the postoperative course was uneventful until the seventh day when she became temporarily apathetic and disoriented At this time the non protein nitrogen was 61 mg per 100 ml, and the creatinine was 3 mg per 100 ml The serum electrolytes were normal, and the patient was transferred to another hospital in a semicomatose, dehydrated state

Physical examination at this time revealed a blood pressure of 140/100, pulse 80, and respirations 18 She was lucid only at intervals, and remained in the hospital for one month during which time her sensorium cleared as nutrition and electrolyte balance were established The non protein nitrogen on the day prior to discharge was 76 mg per 100 ml

While at home she again became confused and vomited frequently She re-entered the hospital on July 29 1955 The red blood count was 3 880 000 the white blood count 11 500 with a normal differential distribution and the hemoglobin 10 5 grams The non protein nitrogen was 92 mg per 100 ml and the CO_2 combining power was 34 2 mEq per liter A trace of albumin and 125 white blood cells per high powered field were present in the urine Hydration and electrolyte balance were re-established, and she was discharged on August 10, 1955 The non protein nitrogen prior to discharge was 68 mg per 100 ml Two weeks later weakness, nausea and vomiting recurred, and she was admitted to a third hospital in a dehydrated semistuporous condition

It was now learned that because of arthritic pains she had been self administering two capsules of Darthronal daily, each capsule containing 50 000 units of vitamin D She was also drinking three to four [illegible] er 100 cc, [illegible] 120 mEq [illegible] per liter [illegible] The serum [illegible] er 100 ml The phenolsulfonphthalein test showed a total excretion of only 15 per cent of the dye in two hours The Sulkowitch reaction was 4 plus Roentgenograms of bone disclosed general osteoporosis and multiple metastatic soft tissue calcification The electrocardiogram showed in

verted T waves in all V leads Electrolyte balance was established by

a normal hemogram normal serum calcium and electrolytes Kidney function tests (phenolsulfonphthalein and urea clearance) were normal. A faint trace of albumin was still present in the urine but the patient was now able to concentrate urine to 1 020 The soft tissue calcifications disappeared but the calcific density within the left kidney remained unchanged

Comment This is a typical example of renal insufficiency resulting from vitamin D intoxication and producing uremic symptoms In addition the impaired renal tubules were vulnerable to the effects of hypochloremic alkalosis resulting from prolonged vomiting thus augmenting acute renal insufficiency Although the patient was chronically and acutely azotemic the entire clinical and biochemical pattern was reversed by cessation of vitamin D and substitution of a low calcium diet Because of the low potassium levels observed in this patient the term potassium losing nephritis could have been applied

Sarcoidosis–Renal Involvement

Hypercalcemia as a manifestation of sarcoidosis was first noted in 1939 by Harrell and Fisher[146] who observed this phenomenon in five of eleven cases Since hypercalcemia is not confined to patients with bone involvement and is often increased to levels not commensurate with the degree of serum protein elevation hypercalcemia must be regarded as a characteristic biochemical disturbance peculiar to sarcoidosis As noted by Albright[8] in this respect sarcoid resembles hyperparathyroidism

Scholz and Keating[328] reported eight cases of sarcoidosis with renal involvement only two of whom manifested renal insufficiency Hypercalcemia was present in six renal calculi in five and nephrocalcinosis in one These authors emphasized the difficulty

differentiating the renal manifestations of sarcoidosis from those hyperparathyroidism

The intensity of the renal insufficiency in all hypercalcemic ates appears directly related to the height and duration of the hy ercalcemia Irrespective of the underlying mechanism, the effects hypercalcemia on the kidney are the same with regard to histo- gic and anatomical changes Granulomatous infiltration of the dneys[27] has also been reported in sarcoidosis but is not regarded a cause of renal insufficiency

Incidence of Renal Involvement in Sarcoidosis

The rarity of renal involvement in sarcoidosis is demonstrated a review of 160 cases of sarcoidosis by Longcope and Frei ian[209] who found only 5 instances of renal insufficiency and 2 istances of renal calculi without renal insufficiency The kidney ilure and hypercalcemia in such cases, however, may so dominate ie clinical pattern as to conceal the underlying disease Two ich cases simulating hyperparathyroidism were reported by Klat kin and Gordon,[180] who were able to collect from the literature nly 17 reports of sarcoidosis with renal failure These authors[180] mphasized the difficulties involved in distinguishing sarcoidosis om hyperparathyroidism, especially in the presence of renal fail re *Since sarcoidosis is a chronic disease characterized by remis ons and exacerbations, and improvement has been noted with eroid therapy, the nephrocalcinosis and azotemia of sarcoidosis ay, in a sense, be considered a potentially reversible type of renal nsufficiency* As pointed out by Phillips and Fitzpatrick,[292] this ype of hypercalcemia deserves emphasis since if unrecognized and ot treated the renal insufficiency may become irreversible

Mechanism of Hypercalcemia

Anderson[15] concluded that since no cases of sarcoidosis and iypercalcemia with a low serum inorganic phosphorus level have een reported, there is strong evidence against parathyroid over ictivity as the cause of hypercalcemia

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Mechanism of Hypercalcemia

Anderson[15] concluded that since no cases of sarcoidosis and hypercalcemia with a low serum inorganic phosphorus level have been reported there is strong evidence against parathyroid overactivity as the cause of hypercalcemia

In Anderson s three cases,[15] calcium balance studies showed that fecal excretion of calcium was less than normal, and an abnormally large urinary excretion of calcium suggested a vitamin D like action, i e, a decrease of tubular reabsorption of calcium The authors[15] demonstrated a hypersensitivity to vitamin D in one patient According to Anderson,[15] cortisone thus corrected the metabolic defect by exerting an action antagonistic to vitamin D Since the serum calcium level is not depressed by cortisone in hyperparathyroidism, Anderson[15] theorized that the administration of cortisone may be of value in the differentiation of hyperparathyroidism from sarcoidosis

Harrell and Fisher,[146] also stated that the bone changes and hypercalcemia of sarcoidosis are not caused by hyperfunction of the parathyroid glands

Dent *et al* [78] reported the case of a 23 year old white male with pulmonary sarcoidosis and renal calculus The blood urea nitrogen was 60 mg per 100 ml, calcium 14 3 mg per 100 ml, phosphorus 4 2 mg per 100 ml, and alkaline phosphatase 11 1 King Arm strong units Moderate band keratitis was observed The treatment consisted of a low calcium diet and 15 mg of cortisone daily The calcium decreased to 10 1 mg per 100 ml and the phosphorus to 2 2 mg per 100 ml, but the alkaline phosphatase remained unchanged A biopsy examination of the kidney during the surgical removal of the renal calculus showed evidence of mild chronic pyelonephritis There was no characteristic sarcoid lesion or tubular calcification The failure of diet to correct the hypercalciuria and hypercalcemia suggested that hypercalcemia results from osseous sarcoidosis and rapid bone destruction According to Dent and his associates,[78] the impairment of renal function cannot be correlated with the severity of the sarcoid process, but seems related to hypercalcemia

Results of Steroid Therapy

Gleckler[125] reported a case of sarcoidosis with hypercalcemia nephrocalcinosis, and renal insufficiency in which intensive cor

sone therapy resulted in a depression of the serum calcium to normal, improvement in renal function (lowering of blood urea nitrogen to 59 mg per 100 ml or to normal), and general well being of the patient Berger and Relman[27] recorded an unusual case of generalized sarcoidosis with clinical evidence of renal insufficiency (non protein nitrogen 75 mg per 100 ml) without hypercalcemia Kidney biopsy disclosed an extensive sarcoid type of granulomatous infiltration and no evidence of tubular calcification Treatment with cortisone resulted in improvement of renal function, and the non protein nitrogen receded to 25 mg per 100 ml Siltzbach[347] reported a considerable degree of objective and subjective improvement in thirteen patients with sarcoidosis treated with cortisone None of these patients however, had renal involvement

The mechanism of the beneficial depression of the calcium level by steroids has not been clarified It was suggested by Soffer[380a] that this response to steroids results from reduced absorption and increased excretion of calcium in the digestive tract

Henneman and his associates [151] in a study of the hypercalcemia of sarcoidosis observed that a fixed low calcium diet combined with cortisone produced a fall in serum and urinary calcium and a rise in fecal calcium Their data substantiate the theory that the hypercalcemia and hypercalciuria of sarcoidosis are in part due to an excessive absorption of calcium from the gastrointestinal tract in a pattern suggesting hypervitaminosis D

Scholz and his associates[329] studied the metabolic effects of cortisone in a 46 year old white male afflicted with diabetes mellitus and sarcoidosis with hypercalcemia and renal insufficiency The diagnosis of sarcoidosis was confirmed by histologic study of a lymph gland removed during the course of a cholecystectomy for cholelithiasis A later renal biopsy revealed no evidence of granulomatous infiltration or pyelonephritis However, spotty calcification of the renal tubules was observed Although the administration of cortisone increased the insulin requirement, it also resulted

in a prompt reduction of the serum calcium with concomitan improvement in renal function (fig 18)

The blood urea nitrogen fell from 128 to 39 mg per 100 ml, an *the serum calcium from 12 5 to 10 1* mg per *100* ml In addition balance studies disclosed a decrease in urinary excretion of calcium and a delayed increase in fecal content of calcium This study further corroborates the theory that improvement of hypercalcemia and renal insufficiency with cortisone results from the reduction of calcium absorption from the gastrointestinal tract and increased excretion of calcium into the gastrointestinal tract Although a transitory increase in blood urea nitrogen was observed on steroid therapy, the blood urea nitrogen ultimately was reduced from a high of 128 mg per 100 ml to 29 mg per 100 ml and the transient rise was attributed to an increased nitrogenous load secondary to the catabolic effects of cortisone The serum calcium, phosphorus and sedimentation rate also approached normal values after treatment These workers, too, emphasize the importance of early recognition and treatment of the hypercalcemia of sarcoidosis to avoid nephrocalcinosis renal calculi, and renal insufficiency

Phillips and Fitzpatrick[292] reviewed the problem of hypercalcemia in a report of two cases of sarcoidosis with symptomatic hypercalcemia which responded well to steroid therapy A mild degree of renal dysfunction, as evidenced by impaired phenol sulfonphthalein excretion and inability to concentrate urine above 1 010, was significantly improved after prolonged treatment Neither of these patients, however, was azotemic or oliguric and, therefore, does not fulfill our criteria on renal insufficiency

Anderson[15] also observed the effect of cortisone on calcium metabolism in patients with sarcoidosis and hypercalcemia In a 14 pear old boy, the pretreatment level of blood urea nitrogen was 54 mg per 100 ml, and the serum calcium was 14 mg per 100 ml After prolonged steroid therapy, the blood urea nitrogen and serum calcium reverted and has been maintained at normal levels with 5 mg of cortisone daily

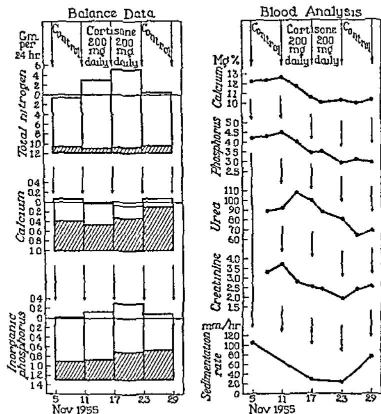


Figure 18 Effects of cortisone on phosphorus calcium and nitrogen balances and on serum calcium inorganic phosphorus and blood urea In these balance data the daily intake is charted from 0 line downward and the average daily excretion (feces below and urine above) upward from the bottom line Extension of the nitrogen calcium or phosphorus above the 0 line indicates a negative balance and a clear space below the 0 line a positive balance (SCHOLZ D A POWER, M H AND DEARING W H Metabolic effects of cortisone in a case of sarcoidosis with hypercalcemia and renal insufficiency Proc Staff Meet Mayo Clinic 32 182–187 19ɔ7)

A 56 year old white female with persistent hypercalcemia and hypercalciuria was subjected to surgical exploration of the neck because a parathyroid tumor was suspected Four normal parathyroids were found, but biopsy examination and an enlarged regional lymph node established the diagnosis of sarcoidosis The blood urea nitrogen rose to 191 mg per 100 ml on one occasion, but did not fall below 132 mg per 100 ml on cortisone therapy despite the return to normal levels of the serum calcium and alleviation of the symptoms of hypercalcemia and renal insufficiency

A 25 year old male with sarcoidosis presented a pretreatment serum calcium level of 14 3 mg per 100 ml and a blood urea nitrogen of 54 mg per 100 ml After steroid therapy, the serum calcium level reverted to normal, pulmonary infiltration cleared, and the blood urea nitrogen was 36 mg per 100 ml All of these patients had clinical manifestations of hypercalcemia i e, polyuria, proteinuria, renal failure, fatigue, weakness, anorexia, nausea, vomiting, weight loss, and all showed the typical corneal changes of hypercalcemia

Hyperchloremic Acidosis

Hyperchloremic renal acidosis[19] is a rare, primary metabolic disturbance of renal tubular function, the cause of which is undetermined It often first becomes apparent during infancy and childhood with episodes of hypopotassemic paralysis osteomalacia, pseudo fractures[7] (Milkman's[248] syndrome), renal calculi, and progressive nephrocalcinosis,[136] ultimately resulting in a fatal uremia The pathogenesis of this tubular defect remains obscure Pyelonephritis[88] has been suspected, but evidence substantiating this theory has not been forthcoming

The syndrome of hyperchloremic acidosis (renal tubular acidosis) was first reported by Lightwood in 1935,[51, 205] and sporadic cases have since appeared in the literature The condition may be congenital, presenting early in life, or it may develop in adults in association with chronic pyelonephritis[400] An iatrogenic form often results from bilateral ureteral transplantation into the bowel[409]

A number of variations of this syndrome have been thoroughly studied and reported by Albright [8]

The basic physiologic disturbance appears to be failure to complete bicarbonate ion absorption by the impaired proximal convoluted tubules The resulting obligatory absorption of bicarbonate by the intact distal tubule inhibits ammonium ion formation and hydrogen ion secretion thus augmenting the urinary depletion of cations (sodium potassium calcium)

Therapy is based upon correction of the acidosis and augmentation of calcium absorption from the gut It appears to us that while this therapeutic regime may correct the acidosis augment calcium absorption and increase calcification of bone it would simultaneously induce further nephrocalcinosis and impairment of tubular function

Since the initial disturbance in this condition is a loss of base all of the depleted cations should be administered in accordance with the need as determined by the biochemical pattern According to Albright [8] the response of these patients to treatment with sodium lactate calcium gluconate potassium citrate and large doses of vitamin D is spectacular Renal insufficiency resulting from the nephrocalcinotic disturbance of tubular function is in part reversible with this treatment [246]

Fanconi Syndrome

When amino aciduria and renal glycosuria are present in addition to the previously described biochemical disturbances characteristic of hyperchloremic acidosis the term Fanconi[102] syndrome is applicable [101, 236] Fanconi[102] first reported this bizarre symptom complex in 1936 as a rare hereditary condition characterized in addition to the above by physical retardation bony changes (rickets) albuminuria a persistently alkaline urine hyperphosphaturia hyperphosphatemia with hypercalcemia hypercalciuria and degenerative changes in the tubules This defect was defined by Fanconi[102] as a failure of reabsorption by the tubules of certain specific solutes from the glomerular filtrate The term amindia

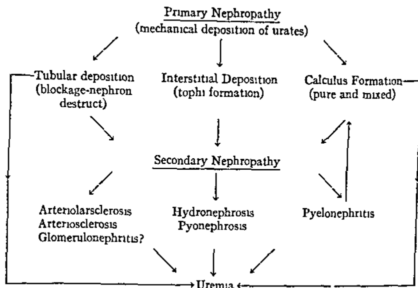


Figure 19 Schematic representation of the types interrelationships and course of gout nephropathy (FINEBERG S K AND ALTSCHUL, A The nephropathy of gout Ann Int Med 44 1182–1194 1956)

sults from the foreign body response to the deposition of urate crystals in the tubules and interstitial tissues Inflammatory and degenerative changes also develop in these areas In the secondary type, uric acid crystals serve as a nidus for the development of nephrolithiasis which predisposes to obstructive uropathy, i e, hydronephrosis pyonephrosis and pyelonephritis

Thus renal impairment results from urate deposits mainly within the lumina and vicinity of the collecting tubules obstructing and destroying the tubular epithelium and producing foci of subacute and chronic pyelonephritis [203]

Lichtenstein *et al* [203] reported on eleven necropsied cases of proven gout All but one of these patients were men in their sixth decade In five the cause of death was uremia These authors corroborate Talbott s observation[374] that the renal manifestations of gout may completely overshadow the minimal arthritis Obstruc

tive nephropathy from uric acid stones was observed in only one of their series

Smith and Lee[354] produced uric acid nephritis in experimental rabbits in an attempt to clarify the mechanism of uric acid injury to the renal epithelium The damaged renal tubules were studied by microdissection techniques Maximal damage was observed in the proximal portion of the collecting tubules They concluded that the local mechanical action of the precipitated urate crystals may be of greater importance than chemical toxic effect

The Nephropathy of Lupus Erythematosus Disseminata

Prior to the advent of steroid therapy patients afflicted with acute subacute and chronic lupus erythematosus disseminata invariably expired rapidly The proper administration of steroids now can prolong indefinitely the life of many of these patients Since considerable improvement of renal function occurs in those patients with renal involvement associated with lupus erythematosus disseminata this condition may be considered among the causes of potentially reversible chronic renal insufficiency [84]

Lupus erythematosus disseminata produces renal damage which is manifest in three ways the most common of which is an insidious rise in blood pressure which is not affected by hormone therapy In this hypertensive group [84] the urine is usually normal at first but within a few months albuminuria white blood cells red blood cells granular and red cell casts and eventually oval fat bodies and broad casts appear In short the condition is characterized by a telescopic urine [331] In the second group the blood pressure remains at upper limits of normal and the above urinary changes appear gradually The third group is characterized by intense pyelonephritis and cystitis

In the acutely ill patient in crisis and in the terminal stages of lupus nephropathy the non protein nitrogen is often considerably elevated During the acute phases of the disease elevations of non protein nitrogen levels up to 130 mg per 100 ml have been reported fully corrected by steroid therapy If evidence of renal

damage and edema persist after a month or more of steroid therapy, then nitrogen mustard and/or triethylene melamine should be administered [84]

In a report of 32 patients with acute disseminated lupus erythematosus treated with steroids, Soffer and his associates[360b] pointed out that the presence of azotemia before institution of treatment may be the result of fever and dehydration and would not necessar ily imply the existence of severe renal damage In four of ten such azotemic patients, the manifestations of renal insufficiency subsided with general clinical improvement These authors indicated how ever, that the persistent evidence of renal insufficiency (azotemia) in adequately treated patients constitutes an ominous prognostic sign

We have had under our care for the past five years, a 42 year old white female with typical symptoms and findings of chronic dis siminated lupus erythematosus treated with large quantities of steroids All of her symptoms abated except the renal manifesta tions, i e, albuminuria and a telescopic' urine demonstrating all types of abnormalities in the sediment There was no biochemical evidence of renal insufficiency During steroid therapy, active pulmonary tuberculosis developed which was cured by six months of sanitarium care and the administration of PAS and INH Since discharge from the sanitarium the urinary sediment has been re markably clear and the quantity of steroids required for control of the underlying disease has been dramatically reduced Whereas previously 30 to 40 mg of Prednisone were needed per day, she now takes only 4 to 5 mg per day, and is asymptomatic We are now in the process of investigating this serendipidous observation

CASE REPORT

The patient a twenty five year old negro chauffeur, entered the West Side Veterans Administration Hospital on September 29 1955, because of severe right flank pain, sweating chills fever, sore throat, and weak ness of three weeks duration Two weeks prior to admission he re ceived considerable quantities of various antibiotics, but the fever did not abate He had lost twenty pounds during this period While in

military service during World War II, he received extensive antiluetic treatment with penicillin because of a positive serology Physical examination disclosed that the patient was both acutely and chronically ill A moderate generalized adenopathy was palpable The temperature was 101 F, blood pressure 105/70, pulse 88, and respirations 20 A moderate degree of diffuse abdominal tenderness was elicited The tip of the spleen was barely palpable Repeated LE preparations disclosed the lupus erythematosus phenomenon in the form of rosettes and LE cells Cryoglobulins were present The non protein nitrogen was 136 [illegible]

to large doses of cortisone was achieved The non protein nitrogen fell to 41 mg per 100 ml and the urine cleared remarkably of albumin and [illegible]

evidence of an extensive lung abscess and despite massive antimicrobial therapy, he expired on December 9 1955 with the symptoms and spinal fluid evidence of a subarachnoid hemorrhage and septic meningitis

Autopsy confirmed the presence of lupus erythematosus disseminata, particularly involving the kidney and further disclosed a large lung abscess which resulted in multiple septic pulmonary vein thrombi and bacterial meningitis from a ruptured mycotic aneurysm The offending organism was staphylococcus

Comment The renal insufficiency associated with disseminated lupus erythematosus was reversed with intensive steriod therapy However, the vulnerability to bacterial infection resulting from prolonged steriod therapy was a factor in the fatal overwhelming infection

Polycystic Disease of the Kidney

The depletion of functioning renal tissue of patients with polycystic kidney disease reduces the physiologic margin of safety to a vulnerable point so that comparatively minor alterations in the internal milieu or renal blood flow result in a profound depression of renal function Thus, in the patient with polycystic disease of

the kidney, a minor degree of shock, dehydration, acidosis, or alkalosis can induce a sudden, intense renal insufficiency which, however, is rapidly reversible by correction of the precipitating disturbance.

It is not unusual to observe a reversal of the uremic state in the patient with polycystic disease with correction of the "extrarenal disturbance, and the patient maintained in a comparatively healthy state for several years. The patient with polycystic disease of the kidneys, for some unexplained reason, is able to withstand chronic renal insufficiency for an unusually long period. Fishberg[149] has pointed out that in his experience, renal insufficiency resulting from polycystic disease is tolerated longer and better than from any other type of renal disease.

In the early stages of polycystic kidney disease, pain of a dull, dragging nature is an outstanding symptom, due probably to the enlarged kidney producing tension on the renal pedicle and pressure on adjacent structures. Occasionally, the pain is colicky in nature and when associated with hematuria simulates renal calculi. Polycystic disease is at times associated with calculi formation and pyelonephritis.

Patients with congenital polycystic kidneys occasionally will manifest no symptoms of renal disease until oliguria and total renal failure emerge. At this stage, symptomatology is more often that of chronic renal insufficiency, i.e., anemia, weakness, lethargy, anorexia, weight loss, vomiting. Hypertension usually develops, but may be absent. Although the polycystic kidney is often palpable, occasionally no renal tumefaction is discernible.

Pathologically and clinically, polycystic disease of the kidney has been divided into two forms, infantile and adult.[348] In the adult form, deterioration of functioning renal tissue progresses slowly, thus permitting longer survival. Also, in the adult form, many of the cysts are tubular in origin and retain some functioning capacity, whereas in the infantile form, the cysts are closed and nonfunctioning.

An excretory urogram presenting considerable elongation and enlargement of the calices is characteristic If tubular damage is advanced however intravenous pyelography may fail to visualize the kidneys More precise visualization of these defects can be obtained on retrograde pyelogram

The association of polycystic kidney disease with congenital intracranial berry aneurysms is well known[363] Four per cent of patients with intracranial aneurysm are said to have polysystic kidneys and 17 per cent of the patients with polycystic kidneys have associated aneurysms It may well be that the hypertension of polycystic kidney disease accelerates the development of berry aneurysms

The Nephropathy of Cushing s Disease

In addition to renal vascular changes and associated hypertension nephrocalcinosis and renal calculi[65] are not infrequently encountered in Cushing s disease Since these renal defects can be corrected and reversed early in the course of the disease by surgical treatment the nephropathy of Cushing s disease may be considered a reversible form of renal insufficiency

The calculus formation and nephrocalcinosis occasionally observed in Cushing s disease are due to the increased protein catabolism with loss of protein bone matrix and resultant osteoporosis hypercalcemia and hypercalciuria Thus although this particular renal lesion might perhaps have been included among hypercalcemic states (Chapter 9) the predominance of renal vascular changes would delineate it as a distinct entity

The frequent occurrence of cardiovascular and renal changes in Cushing s disease was pointed out by Scholz *et al*[330] Vascular alterations in the kidney and the resultant or associated hypertension are the same as those observed in other forms of essential hypertension or benign nephrosclerosis In the more advanced stages of Cushing s disease the hypertension assumes characteristics of a malignant phase and here again the vascular lesions cannot be differentiated from those observed in the malignant phase of hyper

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tension from other causes. As in essential hypertension, the mechanism of these vascular changes and their relationship to hypertension remain obscure

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